Remarks

Claims 4, 6 and 19-21 are pending in this application. Claim 4 has been amended to recite administering to a patient an effective amount of ramipril or ramiprilat, or a pharmaceutically acceptable salt of ramipril or ramiprilat. Support for the added reference to a pharmaceutically acceptable salt of ramipril or ramiprilat appears in the specification, for example, in the fifth full paragraph on page 4. Support for new claims 20-21 appears in the same portion of the specification. Paragraphing has also been added to claim 4 to more clearly recite the claimed invention.

As acknowledged in the Action Summary on page 2 of the Final Office Action, the Examiner withdrew the rejection of claims 4 and 19 as being anticipated by Bussien et al.[1], and also withdrew the rejection of claims 4 and 6 as being anticipated by Webb et al.[2] The Final Office Action, however, raised a new rejection of claims 4, 6 and 19 as having been unpatentable under 35 U.S.C. § 103(a) over Bussien in view of U.S. Patent No. 5,656,603 to Simmons ("Simmons"). In support of the rejection, the Examiner interpreted Bussien as teaching the oral administration of ramipril to normotensive male volunteers, and as suggesting that a certain dose of the compound was expected to be adequate for the treatment of hypertension and congestive heart failure. Office Action at pages 3-4.

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[1] Bussien et al., Naunyn Schmiedeberg's Arch Pharmacol, vol. 329, pp. 63-69 (1985)
[2] Webb et al., Journal of Cardiovascular Pharmacology, vol. 8 (Suppl. 10), pp. S40-S44 (1986)

The Examiner acknowledged that Bussien does not teach the previous medical history of the normotensive male volunteers, but concluded that a person skilled in the art would have been motivated to administer ramipril to normotensive patients regardless of their previous medical history to reduce their chance of developing congestive heart failure. Office Action at page 4. The Examiner also stated that the volunteer patients described in Bussien encompass the limitation in the claims of a patient who has an "essentially maintained heart function." Office Action at page 5. Absent evidence to the contrary, according to the Examiner, there would have been a reasonable expectation of successfully reducing the risk of onset of congestive heart failure as taught by Bussien. Office Action at page 4. Simmons was cited for a teaching that ramipril converts in vivo to ramiprilat. *Id.* The Examiner concluded that to employ ramiprilat would have been obvious since ramiprilat is an active metabolite of ramipril. *Id.*

Applicants respectfully traverse the new rejection. Claim 4, the only independent claim now pending, recites a method for reducing the risk of onset of congestive heart failure in a patient not previously having congestive heart failure and who has an essentially maintained heart function, comprising administering to the patient an effective amount of ramipril or ramiprilat, or their pharmaceutically acceptable salts, wherein the patient is a human who exhibits normal or low blood pressure, and wherein the patient has a history of previous ischaemic heart disease, stroke, or peripheral arterial disease, or has diabetes. In order to establish a *prima facie* case of obviousness of this claim as well as claims 6 and 19-21, the Examiner must show, among other things, that one skilled in the art would have had a reasonable expectation

of success in carrying out that method. *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Moreover, there must be a teaching or suggestion from the prior art of all the claim limitations. MPEP § 2143. As explained below, however, the cited references do not teach all limitations of the claims and one skilled in the art would not have had a reasonable expectation of success in practicing the claimed invention.

Bussien discloses the administration of HOE 498 (ramipril) to normotensive male volunteers ages 21 to 26. *See* Summary on page 63. Nowhere does Bussien inherently or explicitly teach or suggest that the patients have a history of previous ischaemic heart disease, stroke, or peripheral arterial disease, or that they have diabetes. The secondary reference to Simmons does not supply this teaching either, but was simply relied on for a showing that ramipril converts in vivo to ramiprilat. The cited references therefore fail to teach each limitation of the invention and for at least this reason do not create a *prima facie* case of obviousness.

Regarding the element of expectation of success, Bussien does not provide the person skilled in the art with a reasonable expectation that ramipril or ramiprilat (or pharmaceutically acceptable salts thereof) would successfully reduce the risk of onset of congestive heart failure in a patient not previously having congestive heart failure and who has an essentially maintained heart function. Firstly, the conclusions reached in Bussien relate to the potential of ramipril to treat congestive heart failure. Bussien does not suggest the use of ramipril to reduce the risk of onset of that condition. Bussien at page 67, second column, and page 68, first column, last paragraph. Secondly, the prior art as a whole reflected a belief that ACE inhibitors brought about their beneficial effects in the treatment of existing heart failure through their action on functionally impaired

cardiac muscle. A patient having essentially maintained heart function as recited in the present claims would not suffer from such impairment of the cardiac muscle. As a result, there would have been no reasonable basis to expect success in reducing the risk of onset of congestive heart failure in that patient with the ACE inhibitors ramipril or ramiprilat or their pharmaceutically acceptable salts.

A number of clinical trials, and commentaries on those trials, support this interpretation of the state of the art. It is appropriate for applicants to refer to these other studies to illustrate that Bussien and Simmons, when read in context of other art, did not provide the necessary reasonable expectation of success to practice the claimed invention. *See, e.g., In re Dow Chem. Co.*, 5 U.S.P.Q.2d at 1532.

Investigators had previously conducted a "Prevention Trial" and "Treatment Trial" of heart failure as part of the Studies of Left Ventricular Dysfunction ("SOLVD") with the ACE inhibitor enalapril. As the names of the studies imply, the patients in those trials had left ventricular dysfunction, evidenced by the eligibility criteria requiring an ejection fraction of 0.35 or less. Those skilled in the art understand that an ejection fraction of 0.35 or less reflects left ventricular dysfunction and thus a heart function that is not "essentially maintained." In a summary of the "Prevention Trial" reported by The SOLVD Investigators, "Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions," The New England Journal of Medicine, vol. 327, no. 10, pp. 685-691 (1992), the investigators observed "a significant trend toward <u>less benefit from enalapril among patients with a higher ejection fraction</u>" and that "[t]he benefits of enalapril in preventing heart failure and hospitalization were greatest among the patients with the <u>lowest</u>

ejection fraction" (underlining added). *Id.* at page 689, col. 1, lines 13-17 and page 690, col. 2, first full paragraph.[3] The investigators noted a similar trend of "lesser benefit among patients with higher ejection fractions" in the Treatment Trial as well. *Id.* at page 690, col. 2, first full paragraph.

The observation of lesser benefit for patients with higher ejection fractions would not have given one skilled in the art a reasonable expectation of success in expanding the patient population to those having higher ejection fractions and who demonstrate essentially maintained heart function. The investigators of the SOLVD Prevention Trial themselves recommended "that caution be exercised in extrapolating the results of the SOLVD trials to patients with ejection fractions above 0.35." *Id.* at page 690, col. 2, first full paragraph.

The review article of McKelvie et al., "Role of angiotensin converting enzyme inhibitors in patients with left ventricular dysfunction and congestive heart failure," European Heart Journal, vol. 15 (Supp. B), pp. 9-13 (1994), evaluated the results of the SOLVD trials as well as the SAVE trial (studying the effects of the ACE inhibitor captopril in a study with eligibility criteria requiring patients with ejection fractions of 0.40 or less) also counseled against extrapolating the results of the studies:

> Given a tendency towards less benefit in those with lower degrees of LV [left ventricular] dysfunction seen in the SOLVD and SAVE Trials, it would not be prudent to extrapolate the results of these trials to patients with ejection fractions over 40%. Although it appears that the anti-ischaemic effect of ACE inhibitors could potentially be extrapolated to those with relatively preserved left ventricular function, this hypothesis requires verification in prospectively designed studies (underlining added).

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[3] Articles cited in this Amendment have been submitted in Information Disclosure Statements. Applicants nonetheless enclose additional courtesy copies of the documents for the Examiner's reference.

Id. at pages 12-13 under the heading "Limitations of the available data."

Applicants are aware that "absolute predictability" of success is not required to sustain an obviousness rejection, but what is needed instead is a "reasonable expectation" of success. In this field, however, authors of the publications cited above expressly declined to predict success of effects of ACE inhibitors in a patient population that has no evidence of left ventricular dysfunction based on results on patients that do have left ventricular dysfunction.

Additional analysis in Lonn et al., "Emerging Role of Angiotensin-Converting Enzyme Inhibitors in Cardiac and Vascular Protection," Circulation, vol. 90, no. 4, pp. 2056-2063 (1994), also reflects that, at least in the context of this field of medicine, direct proof of successful results in the new patient population was required:

> The evidence provided by the SOLVD and SAVE trials suggests the intriguing possibility that the reduction in ischemic events may occur in a broader group of high-risk patients such as those with preserved left ventricular ejection fraction. However, such patients may not have significant increases in the systemic levels of renin and angiotensin, although activation of the local tissue angiotensin system may occur in response to atherosclerotic vascular injury. <u>It is important, therefore, to provide direct proof of potential benefits of ACE inhibitors in such patients</u> (underlining added).

Id. at page 2063, col. 1-2.

An article published in November of 2004, The PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) Trial Investigators, "Angiotensin-Converting-Enzyme Inhibition in Stable Coronary Artery Disease," The New England Journal of Medicine, vol. 351, pp. 2058-2068 (2004), provides additional evidence that the applicability of the findings in the SOLVD and SAVE trials in patients with left

ventricular dysfunction to a patient population having normal left ventricular function was "conjectural:"

> Since both of these [SOLVD and SAVE] trials were conducted in patients with impaired left ventricular function and presumed activation of the renin-angiotensin system, the applicability of these findings to populations of patients with normal left ventricular function remained conjectural.

Id. at pages 2064-2065 (underlining added).

The Examiner may argue that the clinical trials and commentary discussed above could have made it "obvious to try" those particular ACE inhibitors in patients with no evidence of left ventricular dysfunction. "Obvious to try," however, falls short of the showing needed to render the invention obvious. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995) (" 'Obvious to try' has long been held not to constitute obviousness"). Moreover, "direct proof" in this field was important. In this spirit, the PEACE trial itself was designed to test whether therapy with the ACE inhibitor trandolapril, when added to modern conventional therapy, would reduce the rate of nonfatal myocardial infarction, death from cardiovascular causes, or revascularization in low-risk patients with stable coronary artery disease and normal or slightly reduced left ventricular function. *Id.* at page 2059, col. 1, third full paragraph. The authors ultimately reported that there was no evidence of cardiovascular benefit from the addition of ACE inhibitor therapy:

> In the [PEACE Trial], 8290 patients with stable coronary artery disease and normal or near-normal left ventricular function were randomly assigned to receive trandolapril or placebo; ACE-inhibitor therapy was not found to have a significant benefit. No clinical benefit was observed in the trandolapril group despite the reduction in blood pressure in that group.

Id. at page 2065, third full paragraph.

> The PEACE Trial demonstrates that in a population of patients with coronary artery disease and preserved ejection fraction who receive intensive current standard therapy, usually including coronary revascularization and lipid-lowering agents, and in whom the rate of cardiovascular events is therefore already quite low, there appears to be no evidence of cardiovascular benefit from the addition of ACE inhibitor therapy.

Id. at page 2066, cols. 1-2.

Although the discussion of the PEACE trial as published in the cited article does not constitute prior art, the commentary nonetheless reflects how those skilled in the art would have interpreted the SOLVD and SAVE trials, and how the results of those trials did not create an expectation of success in performing the method of the invention in a patient population having an essentially maintained heart function, and how direct evidence of efficacy in the new patient population was important. For all the reasons explained above, the pending claims would not have been obvious in view of the cited references.

Supplemental Information Disclosure Statements

The applicants enclose a Supplemental Information Disclosure Statement with this Amendment. Applicants also filed a Supplemental Information Disclosure Statement, including Form PTO/SB/08, on January 26, 2005. This earlier Supplemental Information Disclosure Statement appears in the image file wrapper of this application. Applicants respectfully request that the Examiner consider the documents cited in both

Supplemental Information Disclosure Statements and return the initialed forms in the next communication from the Office.

In view of the remarks presented above, applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Please grant any extensions of time required to enter this Amendment and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 13, 2005

By: _____
Steven J. Scott
Reg. No. 43,911

EFFECT OF ENALAPRIL ON MORTALITY AND THE DEVELOPMENT OF HEART FAILURE IN ASYMPTOMATIC PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS

THE SOLVD INVESTIGATORS*

Abstract *Background.* It is not known whether the treatment of patients with asymptomatic left ventricular dysfunction reduces mortality and morbidity. We studied the effect of an angiotensin-converting–enzyme inhibitor, enalapril, on total mortality and mortality from cardiovascular causes, the development of heart failure, and hospitalization for heart failure among patients with ejection fractions of 0.35 or less who were not receiving drug treatment for heart failure.

Methods. Patients were randomly assigned to receive either placebo (n = 2117) or enalapril (n = 2111) at doses of 2.5 to 20 mg per day in a double-blind trial. Follow-up averaged 37.4 months.

Results. There were 334 deaths in the placebo group, as compared with 313 in the enalapril group (reduction in risk, 8 percent by the log-rank test; 95 percent confidence interval, −8 percent [an increase of 8 percent] to 21 percent; P = 0.30). The reduction in mortality from cardiovascular causes was larger but was not statistically significant (298 deaths in the placebo group vs. 265 in the enalapril group; risk reduction, 12 percent; 95 percent confidence interval, −3 to 26 percent; P = 0.12). When we combined patients in whom heart failure developed and those who died, the total number of deaths and cases of heart failure was lower in the enalapril group than in the placebo group (630 vs. 818; risk reduction, 29 percent; 95 percent confidence interval, 21 to 36 percent; P<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (434 in the enalapril group vs. 518 in the placebo group; risk reduction, 20 percent; 95 percent confidence interval, 9 to 30 percent; P<0.001).

Conclusions. The angiotensin-converting–enzyme inhibitor enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations, as compared with the rates in the group given placebo, among patients with asymptomatic left ventricular dysfunction. There was also a trend toward fewer deaths due to cardiovascular causes among the patients who received enalapril. (N Engl J Med 1992;327:685-91.)

ANGIOTENSIN-converting–enzyme inhibitors reduce mortality and the need for hospitalization and improve functional status in patients with symptomatic congestive heart failure.[1-3] Despite such treatment, however, the mortality and morbidity rates associated with this condition are still high. Efforts to prevent the development of heart failure in patients with asymptomatic left ventricular dysfunction are therefore warranted.

Angiotensin-converting–enzyme inhibitors improve the ejection fraction and exercise tolerance in asymptomatic patients with myocardial infarction and low ejection fractions.[4,5] The effects of such drugs on survival, the incidence of heart failure, and the frequency of hospitalization for heart failure are not known, however. This Prevention Trial, a part of the Studies of Left Ventricular Dysfunction (SOLVD), was designed to determine whether an angiotensin-converting–enzyme inhibitor, enalapril, could reduce mortality, the incidence of heart failure, and the rate of related hospitalizations in patients with ejection fractions of 0.35 or less who were not receiving therapy for heart failure (henceforth referred to as patients with asymptomatic left ventricular dysfunction).

Address reprint requests to Dr. Yusuf at the Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Federal Bldg., Rm. 5C08, 7550 Wisconsin Ave., Bethesda, MD 20892.

Supported under contracts from the National Heart, Lung, and Blood Institute and by a gift from Merck Sharp and Dohme, which had no part in the design, conduct, or monitoring of the study or in the analysis, interpretation, or reporting of the results.

*The investigators and institutions participating in the SOLVD study are listed in the Appendix.

METHODS

Organization of the Study

The SOLVD Prevention Trial was a randomized, double-blind, placebo-controlled trial. A total of 4228 patients with asymptomatic left ventricular dysfunction were randomly assigned to receive either enalapril or placebo at one of 83 hospitals linked to 23 centers in the United States, Canada, and Belgium. All data were collected and analyzed at the coordinating center at the University of North Carolina at Chapel Hill. The study was organized and conducted by the project office located at the Clinical Trials Branch of the National Heart, Lung, and Blood Institute and by a steering committee consisting of principal investigators from the centers.[6] An independent Data and Safety Monitoring Board oversaw the progress of the study. The study was approved by the institutional review board of each hospital, and all the patients provided informed consent.

Eligibility of Patients, Run-in Period, and Randomization

Patients known to have heart disease who had ejection fractions of 0.35 or less and who were not receiving diuretics, digoxin, or vasodilators for the treatment of heart failure were eligible for the Prevention Trial. Patients were allowed to receive diuretics for hypertension, digoxin for current or past atrial fibrillation, or nitrates for angina. Details of the measurement of the ejection fraction, exclusion criteria, screening procedure, and the run-in period have been reported previously.[1,6] Patients who had no evidence of overt heart failure at the end of the three-week run-in period, during which they were given enalapril for the first week and placebo for the remainder, were entered into the Prevention Trial. Patients were randomly assigned to receive enalapril at an initial dose of 2.5 mg twice daily, which was gradually increased to 10 mg twice daily unless side effects developed, or a matching placebo. After randomization, the patients were seen after two weeks, six weeks, and four months, and every four months thereafter.

Follow-up and Outcome Measures

At the time of this report, the vital status of four patients in the enalapril group and three in the placebo group was unknown. For all patients not lost to follow-up, information on clinical status, the

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development of heart failure, use of medications other than those prescribed as part of the study, hospitalizations, adherence to the study regimen, and side effects was systematically recorded at each follow-up visit. For patients who died, were hospitalized, or had heart failure, the cause of death, the primary reason for hospitalization, and the development of heart failure were ascertained and classified by the principal investigator at each center, who was unaware of the patients' treatment, using standardized forms. Four overlapping definitions of heart failure, of increasing severity, were used: (1) heart failure, identified by the study physician on the basis of symptoms, signs, or the need for changes in therapy; (2) heart failure requiring the addition of a diuretic, digoxin, or a vasodilator to the patient's regimen (in the case of patients already receiving any one of these drugs at base line, the additional drug had to be prescribed for this indication); (3) heart failure requiring hospitalization; and (4) progressive heart failure causing death. When heart failure developed, the patients' physicians could use treatments at their discretion, but it was recommended that angiotensin-converting–enzyme inhibitors be used only after other drugs had been tried.

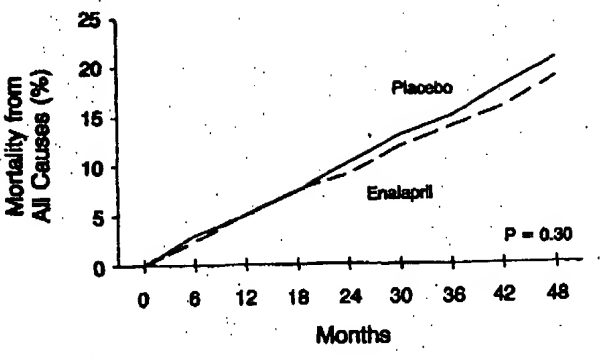
Table 1. Base-Line Clinical Characteristics and Drug Therapy, According to Treatment Group.

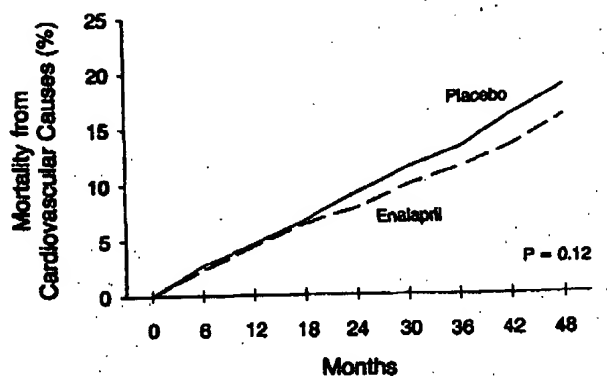
Characteristic	Placebo (N = 2117)	Enalapril (N = 2111)
	mean value	
Age (yr)	59.1	59.1
Weight (kg)	81.6	80.9
Ejection fraction	0.28	0.28
Blood pressure (mm Hg)		
Systolic	125.6	125.3
Diastolic	78.0	77.9
Heart rate (beats/min)	75.2	74.6
Serum sodium (mmol/liter)	140.2	140.3
Serum potassium (mmol/liter)	4.4	4.3
Serum creatinine (mg/dl)*	1.2	1.2
	% of group	
Male sex	88.6	88.5
Race		
White	86.5	86.4
Black	9.7	9.2
Other	3.4	4.1
NYHA functional class†		
I	67.1	66.3
II	32.7	33.4
History		
Ischemic heart disease	82.9	83.5
Myocardial infarction	79.4	80.5
Hypertension	37.3	36.8
Diabetes mellitus	15.1	15.4
Idiopathic dilated cardiomyopathy	10.1	8.6
Cigarette smoking‡	24.1	22.8
Angina‡	33.8	33.8
Atrial fibrillation‡	4.0	3.9
Cardiothoracic ratio >0.50	40.2	39.6
Drug therapy		
Neither digoxin nor diuretics	72.3	74.9
Digoxin	13.2	11.7
Diuretics	17.0	16.2
Potassium-sparing diuretic	4.0	3.9
Any vasodilator	45.7	47.1
Nitrates	29.9	30.6
Antiarrhythmic drugs	15.7	14.4
Beta-blockers	23.7	24.3
Calcium-channel blockers	34.1	35.6
Anticoagulant agents	12.3	11.2
Antiplatelet agents	52.7	55.7
Potassium supplements	6.4	5.5

*To convert values to micromoles per liter, multiply by 88.4.

†Five patients in NYHA class III were inadvertently enrolled in the Prevention Trial and have been retained in the analyses. No deaths or hospitalizations occurred among these five patients.

‡At base line.





Placebo	2117	2054	2009	1854	1566	1234	934	627	399
Enalapril	2111	2059	2000	1837	1580	1244	955	684	436

Figure 1. Total Mortality (Upper Panel) and Mortality from Cardiovascular Causes (Lower Panel) in the Prevention Trial.

The numbers at the bottom of the figure are the numbers of patients in each group who were alive at base line and after each six-month period.

Statistical Analysis

The primary hypothesis of the Prevention Trial was that enalapril would reduce total mortality. A subsidiary hypothesis was that enalapril would reduce the incidence of heart failure and the rate of hospitalization for heart failure. The last two end points were combined with mortality to avoid the problem of competing risks.[7] Such analyses are more conservative and methodologically more correct than analyses of secondary outcomes alone. However, data on the incidence of heart failure and hospitalization are also provided in the tables. A one-sided test with a significance level of 0.025 (equivalent to a nominal two-sided P value of 0.05) was specified in the protocol; however, at the request of the *Journal*, two-sided significance levels are reported. We estimated that a sample of 4100 patients followed for an average of three years would provide a 90 percent power to detect a 25 percent reduction in mortality.[1,6] The sample size was increased to 4600 in order to protect against unexpectedly low event rates or poor compliance. We recruited 4228 patients from July 1986 through May 1990. A termination date of August 31, 1991, was set for the study in advance. Deaths occurring between the patients' final follow-up visits and this date are also

reported. Details of monitoring, adjustment of the critical z value, and tests for heterogeneity have been reported earlier.[1] A stratified log-rank statistic was used to compare the life-table survival curves and the development of heart failure for all patients randomly assigned to the two groups.[8,9]

Results

The clinical characteristics of the two study groups were similar at base line (Table 1). The mean left ventricular ejection fraction was 0.28; 67 percent of the patients were in New York Heart Association (NYHA) functional class I, and 33 percent were in class II; one third of the patients had angina, and 74 percent were not receiving diuretics or digoxin for any reason. The average follow-up was 37.4 months (range, 14.6 to 62.0).

Mortality

There were 334 deaths in the placebo group, as compared with 313 in the enalapril group, for a reduction in risk of 8 percent as calculated from the log-rank test (95 percent confidence interval, −8 percent [an increase of 8 percent] to 21 percent; P = 0.30) (Fig. 1 and Table 2). The difference was entirely due to a reduction in deaths due to cardiovascular causes (298 in the placebo group, as compared with 265 in the enalapril group; risk reduction, 12 percent; 95 percent confidence interval, −3 to 26 percent; P = 0.12). Among the deaths from cardiovascular causes, the difference in mortality between the groups was observed mainly in terms of those classified as due to progressive heart failure (106 in the placebo group vs. 85 in the enalapril group); there was little difference between the groups in the number of deaths presumed to be due primarily to arrhythmia (105 vs. 98).

Hospitalization for Heart Failure

Altogether, 518 patients in the placebo group (24.5 percent) and 434 in the enalapril group (20.6 percent) died or were hospitalized for new or worsening heart failure (risk reduction, 20 percent; 95 percent confidence interval, 9 to 30 percent; P<0.001) (Table 2 and Fig. 2). By one year, there had been 218 such events in the placebo group (10.3 percent), as compared with 167 in the enalapril group (7.9 percent) (risk reduction, 25 percent; 95 percent confidence interval, 8 to 38 percent). After one year there were a further 300 such events among the 1899 remaining patients in the placebo group (15.8 percent), as compared with 267 among the 1944 in the enalapril group (13.7 percent).

There were 454 hospitalizations for heart failure in the placebo group, as compared with 306 in the enalapril group; 102 patients in the placebo group (4.8 percent) and 58 patients in the enalapril group (2.7 percent) were hospitalized more than once for worsening heart failure (risk reduction, 44 percent; 95 percent confidence interval, 23 to 59 percent). The median length of time to the first hospitalization for heart failure was 13.2 months in the placebo group. The length of time before there were a similar number of hospitalizations in the enalapril group was 27.8 months.

Development of Heart Failure

In the placebo group, 818 patients had heart failure or died (38.6 percent), as compared with 630 in the enalapril group (29.8 percent) (Fig. 2) (risk reduction, 29 percent; 95 percent confidence interval, 21 to 36 percent; P<0.001). The median length of time to the development of heart failure was 8.3 months in the placebo group. The length of time to the development of a similar number of events in the enalapril group was 22.3 months. Significant reductions in the incidence of heart failure were observed regardless of the definition of heart failure used. The difference in the rates of heart failure was seen as early as three months after randomization (143 patients in the pla-

Table 2. Deaths, Causes of Death, Development of Heart Failure, and Hospitalizations for Heart Failure, According to Treatment Group.

Cause of Death or Type of Event	Placebo (N = 2117)	Enalapril (N = 2111)	Reduction in Risk (95% CI)*	z Score	P Value†
	no. (%)		%		
Death‡					
All causes	334 (15.8)	313 (14.8)	8 (−8 to 21)	1.02	0.30
Cardiovascular causes	298 (14.1)	265 (12.6)	12 (−3 to 26)	1.57	0.12
Cardiac	271 (12.8)	238 (11.3)	13 (−3 to 27)	1.63	0.10
Arrhythmia without worsening CHF	105 (5.0)	98 (4.6)	7 (−22 to 30)	0.54	NS
Progressive heart failure (pump failure or arrhythmia with CHF)	106 (5.0)	85 (4.0)	21 (−5 to 41)	1.64	0.10
Myocardial infarction	52 (2.5)	46 (2.2)	14 (−28 to 42)	0.74	ND
Other	8 (0.4)	9 (0.4)	—	—	ND
Stroke	13 (0.6)	10 (0.5)	—	—	ND
Other vascular cause or unknown	14 (0.7)	17 (0.8)	—	—	ND
Noncardiovascular causes	36 (1.7)	48 (2.3)	—	—	ND
Morbidity and combined outcomes					
Development of CHF	640 (30.2)	438 (20.7)	37 (28 to 44)	7.47	<0.001
Development of CHF and anti-CHF therapy	477 (22.5)	293 (13.9)	43 (33 to 50)	7.59	<0.001
First hospitalization for CHF	273 (12.9)	184 (8.7)	36 (22 to 46)	4.65	<0.001
Multiple hospitalizations for CHF	102 (4.8)	58 (2.7)	44 (23 to 59)	3.61	<0.001
Death or development of CHF	818 (38.6)	630 (29.8)	29 (21 to 36)	6.55	<0.001
Death or hospitalization for CHF	518 (24.5)	434 (20.6)	20 (9 to 30)	3.46	<0.001

*By the log-rank test. CI denotes confidence interval. A negative number indicates an increase in risk.

†NS denotes not significant, and ND not done (i.e., no statistical test was performed).

‡After August 31, 1991, but before the final follow-up visits, there were eight additional deaths in the placebo group and four in the enalapril group. Therefore, the total numbers of deaths were 342 in the placebo group and 317 in the enalapril group (risk reduction, 9 percent; z = 1.23; P = 0.22). The corresponding numbers for mortality from cardiovascular causes were 304 and 269 (risk reduction, 13 percent; 95 percent confidence interval, −2 to 26; z = 1.71; P = 0.09). CHF denotes congestive heart failure.

cebo group vs. 82 in the enalapril group), and the groups continued to diverge until the end of the study.

The Development of Heart Failure and Hospitalization for Heart Failure in Relation to Subsequent Mortality

The difference in mortality between the groups was attributable only to the lower incidence of heart failure among patients assigned to enalapril (Table 3); 156 patients in the placebo group and 121 in the enalapril group died after heart failure developed (mortality among patients with heart failure, 24.4 percent and 27.6 percent, respectively). Among patients who did not have heart failure, the mortality rates were 12.1 percent in the placebo group and 11.5 percent in the enalapril group. Similar analyses of deaths among patients who died after hospitalization for heart failure (89 deaths in the placebo group and 63 in the enalapril group) also demonstrated a difference, whereas there was little difference in mortality among patients not hospitalized for heart failure (245 deaths in the placebo group and 250 in the enalapril group). Therefore, the difference in the incidence of heart failure accounted for the lower mortality with enalapril. However, 40.9 percent of the patients in the placebo group who had heart failure subsequently received an angiotensin-converting–enzyme inhibitor.

Table 3. Mortality and Use of Angiotensin-Converting–Enzyme (ACE) Inhibitors at the End of the Study Period among Patients Who Had Congestive Heart Failure (CHF) or Patients Hospitalized for CHF, As Compared with Patients without CHF or Hospitalization.

Variable	Patients with CHF		Patients without CHF		Patients Hospitalized for CHF		Patients Not Hospitalized for CHF	
	Placebo	Enalapril	Placebo	Enalapril	Placebo	Enalapril	Placebo	Enalapril
No. of patients	640	438	1477	1673	273	184	1844	1927
Died								
No.	156	121	178	192	89	63	245	250
Percent	24.4	27.6	12.1	11.5	32.6	34.2	13.3	13.0
Alive								
No.	484	317	1299	1481	184	121	1599	1677
Percent	75.6	72.4	87.9	88.5	67.4	65.8	86.7	87.0
Use of ACE inhibitors*								
No.	262	147	134	107	139	89	257	165
Percent	40.9	33.6	9.1	6.4	50.9	48.4	13.9	8.6
Average mo. of follow-up†	27.7	25.8	36.0	36.6	25.3	22.1	36.9	37.2

*Includes those receiving open-label ACE inhibitors.

†For patients in whom CHF developed or who were hospitalized for CHF, the duration of follow-up is calculated from time of the event to the end of the trial. For those without an event, follow-up is calculated from randomization to the end of the trial.

The rate of mortality among patients who were hospitalized for heart failure (regardless of their treatment assignment) was about 33 percent, as compared with 13 percent among those who had not been hospitalized by the end of the study. After adjustment for differences in length of follow-up, the relative risk of death at one year among those who were hospitalized, as compared with those who were not hospitalized, was 4.6 (95 percent confidence interval, 3.4 to 6.3), indicating that hospitalization for heart failure was associated with a substantially higher risk of death.

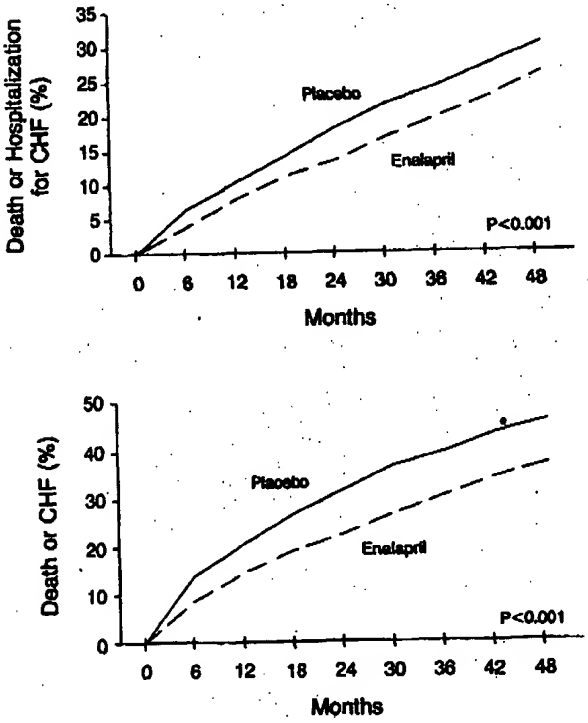


Figure 2. Death or Hospitalization for Congestive Heart Failure (CHF) and Death or Development of Heart Failure in the Prevention Trial.

See Figure 1 for the numbers of patients at risk at each time point.

All Hospitalizations

Altogether, 967 patients in the placebo group (45.7 percent) and 876 in the enalapril group (41.5 percent) were hospitalized primarily for a cardiovascular reason ($P = 0.006$), whereas 534 patients in the placebo group (25.2 percent) and 595 patients in the enalapril group (28.1 percent) were hospitalized for a noncardiovascular reason. The total number of patients hospitalized for any reason was 1202 in the placebo group, as compared with 1167 in the enalapril group ($P = 0.34$). The total number of hospitalizations was 2839 in the placebo group and 2645 in the enalapril group ($P = 0.12$).

Outcomes in Subgroups

The effect of treatment on various outcome measures was examined in several subgroups specified by the protocol; these were defined by base-line serum sodium levels, use of vasodilators, ejection fraction, and cause of ventricular dysfunction. We also exam-

ined the effects of treatment among patients with no functional disability (NYHA functional class I) and among those who were not receiving digoxin or diuretics at entry. Because the overall results regarding mortality in the Prevention Trial did not reach conventional levels of statistical significance, analysis of mortality in subgroups is less reliable than similar analyses of data on the rates of heart failure or hospitalizations for heart failure. There was a significant trend toward less benefit from enalapril among patients with a higher ejection fraction (Fig. 3). The benefits of treatment in terms of the frequency of hospitalization or the development of heart failure were consistent in most of the other specified subgroups. The benefits among those who were not receiving digoxin or diuretics (reduction in the frequency of death or hospitalization, 25 percent [95 percent confidence interval, 12 to 36 percent]; reduction in the incidence of heart failure, 39 percent [95 percent confidence interval, 29 to 47 percent]) and among those in functional class I (reduction in mortality or hospitalization, 21 percent [95 percent confidence interval, 7 to 33 percent]; reduction in mortality or development of heart failure, 28 percent [95 percent confidence interval, 18 to 37 percent]) were similar to the overall results.

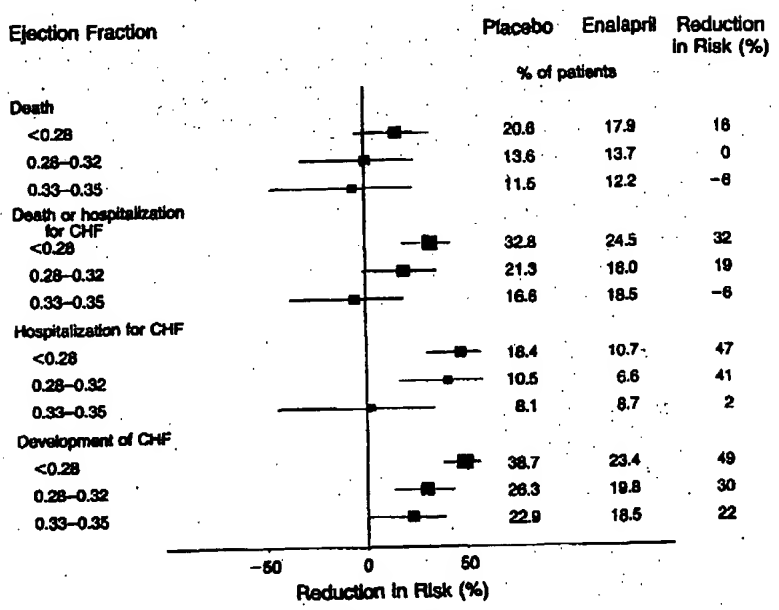


Figure 3. Effect of Enalapril on Mortality, Incidence of Congestive Heart Failure (CHF), and Hospitalization for Heart Failure in Various Subgroups Defined According to the Ejection Fraction.

Each subgroup composes one third of the study population. For each subgroup, the reduction in risk with enalapril is shown as a percentage (squares). (A negative value for risk reduction indicates an increase in risk.) The horizontal lines indicate the 95 percent confidence intervals. The size of each square is proportional to the number of events in the subgroup. The vertical line corresponds to a finding of no effect. The chi-square statistic for the interaction of the ejection fraction with the effect of enalapril on the risk of death was 2.16 ($P = 0.34$); that for the interaction with the effect of enalapril on the combined end point of death or hospitalization for CHF was 9.30 ($P = 0.009$); that for the interaction with its effect on hospitalization for CHF alone, 8.76 ($P = 0.012$); and that for the interaction with its effect on the development of CHF, 9.87 ($P = 0.007$).

Adherence to the Study Regimen, Side Effects, and Changes in Blood Pressure, Serum Electrolyte Levels, and Renal Function

The final mean daily dose of enalapril among all randomized patients was 12.7 mg. Among the patients in the enalapril group who were taking enalapril, the mean daily dose was 16.7 mg. At the last visit, 1.9 percent of the enalapril group was receiving 2.5 mg daily, 6.9 percent was receiving 5 mg daily, 11.1 percent was receiving 10 mg daily, and 56.1 percent was receiving 20 mg daily. Twenty-four percent of the patients in the enalapril group and 27 percent in the placebo group had stopped taking blinded medication by the end of the study. The study medication was discontinued in 218 patients in the placebo group and 102 in the enalapril group because of worsening heart failure. More patients were receiving diuretics and digoxin in the placebo group than in the enalapril group at one year (diuretics: 30 percent vs. 22 percent; digoxin: 19 percent vs. 15 percent), at two years (diuretics: 33 percent vs. 24 percent; digoxin: 23 percent vs. 17 percent), and at three years (diuretics: 35 percent vs. 27 percent; digoxin: 24 percent vs. 18 percent).

A high proportion of patients in both groups reported side effects during the trial (76 percent in the enalapril group vs. 72 percent in the placebo group). There were significantly more reports of dizziness or fainting (45.8 percent vs. 39.2 percent) and cough (33.8 percent vs. 27.3 percent) in the enalapril group. There was no difference in the frequency of angioedema (1.4 percent in each group); most cases of angioedema were mild and did not require the discontinuation of medication. Overall, 8 percent of the patients in the enalapril group and 45 percent in the placebo group permanently discontinued the study medication because of side effects. Forty-three patients in the enalapril group and 41 in the placebo group were given a diagnosis of cancer. Of these, 19 patients in the enalapril group and 13 in the placebo group were identified as having a cancer of the gastrointestinal tract, liver, gallbladder, or pancreas.

When averaged over all follow-up visits, systolic and diastolic blood pressures were significantly lower in the enalapril group than in the placebo group (by 5.2 and 3.2 mm Hg, respectively). Serum potassium and creatinine levels were slightly but significantly

higher in the enalapril group (by 0.1 mmol per liter and 0.04 mg per deciliter [3.5 μmol per liter], respectively).

Discussion

Although a significant reduction in total mortality with enalapril treatment was not observed in the Prevention Trial, enalapril, an angiotensin-converting–enzyme inhibitor, significantly reduced the incidence of heart failure and the need for hospitalizations for heart failure among patients with asymptomatic left ventricular dysfunction. There was also a trend (albeit not a significant one) toward fewer deaths due to cardiovascular causes. Although the relative reductions in total mortality and mortality from cardiovascular causes were smaller in the Prevention Trial (8 percent and 12 percent, respectively) than in the previously reported Treatment Trial (16 percent and 18 percent, respectively),[1] the direction of the effects was similar in both trials. However, the effects on the frequency of hospitalization for heart failure (a 36 percent reduction in both trials) and deaths from progressive heart failure (a 19 percent reduction in the Treatment Trial and a 21 percent reduction in the Prevention Trial) were similar.

The effect of enalapril in preventing the development of heart failure was evident as early as six weeks after randomization, and the difference between the two groups continued to increase until the end of the study. Similar results were observed for the rates of hospitalization for heart failure and death. After the development of heart failure or after hospitalization for heart failure, the mortality rates increased substantially as compared with those in patients in whom heart failure had not developed. This difference indicates that the development of heart failure has a serious adverse effect on prognosis.[10]

There were consistent reductions in the proportion of patients hospitalized for cardiovascular reasons in both the Treatment Trial and the Prevention Trial. There was a significant reduction in the proportion of patients in the enalapril group hospitalized for noncardiovascular reasons in the Treatment Trial,[1] whereas the opposite was observed in the Prevention Trial. The contradictory differences in the frequency of hospitalization for noncardiovascular reasons are probably due to chance. In the two trials combined, the number of hospitalizations for noncardiovascular reasons was virtually identical in the two groups (996 in the placebo groups vs. 997 in the enalapril groups). No significant difference in hospitalizations in any specific noncardiovascular category was observed in either trial.

During the study, more patients randomly assigned to the placebo group than to the enalapril group received digoxin, diuretics, or angiotensin-converting–enzyme inhibitors that were not part of the study regimen. In all, 40.9 percent of patients in whom heart failure developed and 50.9 percent of those who were hospitalized in the placebo group were prescribed an angiotensin-converting–enzyme inhibitor, generally after the development of heart failure. Because the reduction in mortality with enalapril was chiefly attributable to a lower incidence of heart failure, the frequent use of angiotensin-converting–enzyme inhibitors and perhaps other drugs in this group is likely to have led to the underestimation of the reduction in mortality with enalapril. Our data can also be interpreted as indicating that there may be only a small difference in mortality between asymptomatic patients treated preventively and those treated with careful follow-up and initiation of therapy if heart failure develops.

The reductions in the frequency of hospitalization and the incidence of heart failure were of approximately the same magnitude among patients who were receiving diuretics or digoxin at entry and those who were not receiving such agents; the reductions were also similar among patients in NYHA functional classes I and II. The benefits of enalapril in preventing heart failure and hospitalization were greatest among the patients with the lowest ejection fractions. Similar trends toward lesser benefit among patients with higher ejection fractions were observed in the SOLVD Treatment Trial,[1] suggesting that caution be exercised in extrapolating the results of the SOLVD trials to patients with ejection fractions above 0.35.

The major side effects observed in this study — hypotension, cough, and elevated serum potassium levels — are similar to those observed in the SOLVD Treatment Trial and other trials of angiotensin-converting–enzyme inhibitors in similar patients.[1-3] The frequency of side effects in the SOLVD trials may be higher than in other studies because of our substantially longer follow-up and the fact that patients were asked about these side effects at each visit. The proportion of patients who reported skin rashes, taste disturbances, or any other side effect was no higher in the enalapril group than in the placebo group in either SOLVD trial. The excess rate of gastrointestinal cancer is similar to that observed in the Treatment Trial.[1] When the data from both trials were combined, there were 38 cases of gastrointestinal cancer in the enalapril group as compared with 22 in the placebo group. Although this difference would be nominally significant when taken in isolation, this was one of numerous comparisons and the tests of significance are therefore less reliable. The frequency of these cancers did not increase with longer drug exposure (there were 20 cases in the first two years and 18 thereafter in the enalapril group, as compared with 12 and 10 in the placebo group), and the cancers were widely dispersed throughout the gastrointestinal tract (rectum, cecum, and colon: 26 in the enalapril group vs. 17 in the placebo group; esophagus and stomach: 5 vs. 1; gallbladder, pancreas, and liver: 7 vs. 4). For these reasons, the excess gastrointestinal cancers in the enalapril group were probably not causally related to the study treatment but rather a chance finding. It would be prudent, how-

ever, to examine this relation in other studies.

In the SOLVD Prevention Trial, enalapril was well tolerated by patients with asymptomatic left ventricular dysfunction; it reduced the incidence of heart failure and related hospitalizations, with a trend toward fewer cardiovascular deaths. However, the lack of a statistically significant effect on overall mortality or on the rate of deaths presumed to be due to arrhythmia emphasizes the need to explore more effective means, or additional means, of treating patients with left ventricular dysfunction.

Appendix

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European Heart Journal (1994) **15** (*Supplement B*), 9–13

Role of angiotensin converting enzyme inhibitors in patients with left ventricular dysfunction and congestive heart failure

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KEY WORDS: Converting enzyme inhibitor, heart failure, mortality, morbidity, heart failure trials.

We now have conclusive data that ACE inhibitors reduce mortality, morbidity, and symptoms in patients with low ejection fraction and/or heart failure. Therefore, ACE inhibitors should be routinely used in all such patients, as long as there are no clear contraindications. Routine use of ACE inhibitors will lead to prolongation of survival and a reduction in the number of hospitalizations for heart failure and ischaemic events. The reduction in costs associated with the prevention of these events is likely substantially to offset the cost of the use of these therapies. Therefore, ACE inhibitors should be instituted as early as possible in patients with LV dysfunction.

Introduction

Congestive heart failure (CHF) is a major and growing public health problem. Over two million individuals in the United States are estimated to suffer from CHF and the proportion may be 10 to 15 times this worldwide[1]. The number of patients with CHF is expected to increase over the next few decades, due partly to the survival of high risk patients following myocardial infarction (MI), hypertension, to the extension in survival of individuals with CHF and to the ageing of the population.

Based on the Framingham Heart Studies results published some 20 years ago, the one year mortality in patients with CHF was reported to be approximately 15% to 20%[2]. However, more recent data from Framingham indicate that as the population has aged mortality in patients with heart failure in the community at one year is approximately twice what was originally estimated. In the United States and Canada, CHF is the commonest cause of hospital admission in individuals over the age of 65 years[1]. Based on the SOLVD registry, it appears that approximately 30% of patients are admitted to hospital each year[3] and of these, approximately 30% attend more than once during the year. The most common cause of death or hospitalization in these patients is worsening heart failure, which accounts for approximately 40% to 50% of all deaths[4]. A further significant proportion of mortality/morbidity is due to arrhythmic or ischaemic events[4–6]. In addition, patients with heart failure are at higher risk of developing stroke or suffering major thromboembolic events, such as pulmonary embolism or peripheral embolic events. A higher incidence of developing lung infections, such as pneumonia and bronchitis, has also been found in patients with CHF, who not only have high annual mortality and hospitalization rates, but also significant impairments of quality of life, functional capacity, activities of daily living, and more often manifest depression, anxiety and reduced life expectations.

These varied complications result in numerous reasons for hospital admission and death and, therefore, indicate that a multi-factorial approach is needed to treat patients with heart failure. A comprehensive discussion of CHF treatment is beyond the scope of this paper. We will, however, review the major trials which have examined the effects of angiotensin converting enzyme inhibitors (ACE inhibitors) in patients with heart failure and asymptomatic left ventricular (LV) dysfunction.

Role of ACE inhibitors in preventing clinically relevant outcomes

MORTALITY

The impact of ACE inhibitors has been evaluated in patients with LV dysfunction, CHF and following MI. The SOLVD and SAVE trials, along with the first CONSENSUS trial, have conclusively demonstrated that ACE inhibitors reduce mortality in patients with heart failure and left ventricular dysfunction. The SOLVD Prevention Trial showed a trend towards fewer cardiovascular deaths, but this trend did not reach conventional levels of statistical significance[7]. In the SAVE Trial, approximately 50% of patients were on diuretics or digoxin at randomization and the observed significant reduction in cardiovascular mortality was consistent in both subgroups, i.e. those on and not on anti-failure therapy at baseline[5]. This suggests that background anti-failure therapy does not significantly modify the effect of ACE inhibitors. Therefore, the combined data from SOLVD and SAVE indicate that ACE

The research described in this article was largely supported by the National Heart Lung and Blood Institute, U.S., with continuing support from the Medical Research Council of Canada.

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0195–668X/94/ 0B0009+ 05 $08.00/0

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inhibitors are of benefit not only in patients with overt heart failure, but also in those with asymptomatic left ventricular dysfunction. In the two trials that included patients with overt heart failure, the SOLVD Treatment Trial and the CONSENSUS I Trial, there was an immediate reduction in mortality with the institution of ACE inhibitor therapy, with the benefits being sustained for up to 4 years. In patients with asymptomatic LV dysfunction, such as those enrolled in the SOLVD Prevention Trial and those enrolled in the SAVE Trial, benefits were not observed for at least a year to 18 months; thereafter mortality was reduced during the rest of the long-term treatment in the trial. This indicates that there may be a period during which LV remodelling has to be prevented in asymptomatic LV dysfunction, in order to limit the development of heart failure. This ultimately translates into a reduction in mortality.

Importantly, the SOLVD Prevention Trial and SAVE have established that ACE inhibitor therapy may be beneficial in patients who develop asymptomatic left ventricular dysfunction after an MI whether initiated a few days after the event (SAVE) or deferred up to one year (SOLVD). In the CONSENSUS II Trial, in which approximately 6000 patients with AMI (no selection based on presence of heart failure or ventricular dysfunction) were randomized to receive enalapril or placebo, there was no decrease in mortality[8]. This trial was stopped early because of a tendency towards a greater number of deaths in patients receiving enalapril compared to those receiving placebo, so that the possibility of demonstrating a significant reduction in mortality was low. However, the result of this trial are consistent with the possibility of a 10% to 15% benefit.

CONSENSUS II had a short follow-up period of 6 months and did not select patients with LV dysfunction or heart failure, and these may be reasons why no significant difference was observed for enalapril. Alternatively, neurohormonal adaptions may be important to the acute compensation in the first hours to days post myocardial infarction. In CONSENSUS II, subgroups where greatest benefits could be anticipated (e.g. large anterior MI, history of previous MI or heart failure complicating index infarction) did not realize a risk reduction with early ACE inhibitor[8].

It has been shown from the SOLVD Prevention Trial and SAVE (patients with low ejection fraction (EF)) that it takes 10–18 months for an effect to be observed. More recently, the AIRE study with AMI patients with heart failure, indicated a significant reduction in mortality with long-term treatment with ramipril compared to placebo[9]. The effects of ACE inhibitors in patients with AMI will be clarified by the collective data from three very large trials, ISIS-4 (Fourth International Study of Infarct Survival), GISSI-3 (Third—Gruppo Italiano per lo Studio della Streptochinasi nell Infarcto Miocardico), and a large Chinese study which included about 90 000 patients.

HEART FAILURE AND HEART FAILURE HOSPITALIZATIONS

In the SOLVD Prevention Trial, ACE inhibitors reduced the incidence of heart failure by 37%[7]. The prevention of heart failure was observed for various severities and definitions of heart failure, including heart failure diagnosed by the study physician, heart failure requiring the initiation of diuretics or digoxin (43% decrease), heart failure requiring hospitalization (36% decrease), and a trend towards deaths due to heart failure (21% decrease). In addition to the prevention of heart failure in the SOLVD Prevention Trial, there were clear reductions in hospital admissions for heart failure (33% reduction). This reduction was also seen in the SOLVD Treatment Trial[10] and in the SAVE Trial[5]. In all three trials there was also a reduction in multiple hospitalizations per subject in the ACE inhibitor group. These results were highly significant and collectively indicate that ACE inhibitors prevent clinical deterioration, symptomatic worsening and hospitalization for heart failure. Table 1 demonstrates the number of events prevented or delayed by treating 1000 patients with ACE inhibitors for 3 years. As can be seen, ACE inhibitors have a significant impact on development of heart failure, hospitalizations, and ischaemic events in either the group with no heart failure but EF < 0·35 or the heart failure group with EF < 0·35. These data, therefore, suggest that the use of ACE inhibitors could lead to a substantial reduction in health care costs.

Table 1 Implications of routine use of ACE inhibitors in patients with low ejection fractions (based upon the SOLVD trial results)

	Number of events prevented or delayed by treating 1000 patients with an angiotensin-converting enzyme inhibitor for 3 years	
	EF ≤ 0·35 + CHF	EF ≤ 0·35 + no CHF
Development of CHF	N/A	90
Hospitalization for CHF	200	65
Myocardial infarction or unstable angina	50	15

CHF = congestive heart failure; EF = ejection fraction; N/A = not applicable.

Ischaemic events

In both the SOLVD and SAVE trials, the occurrence of an interim myocardial infarction increased the risk of subsequent deaths by up to eight-fold. In the SOLVD trials, one third of all deaths were preceded by a major ischaemic event. Therefore, reductions in ischaemic events should be an integral part of the management of patients with LV dysfunction. In the SOLVD trials, 25% of patients in the placebo group developed MI or were hospitalized for unstable angina during the 3·5 years of follow-up[11]. Treatment with an ACE inhibitor, enalapril, reduced the incidence of MI by 23% (P = 0·001), and hospital admissions for unstable angina by 22% (P = 0·001).

The reduction in MI was seen for both fatal and non-fatal events, although the effects of reducing non-fatal infarction were twice as great as reducing fatal MI. Prevention of MI was also observed in the SAVE trial, where captopril reduced the risk of this event by approxi-

mately 25%[5]. In the SAVE trial, there was also a significant reduction in the need for revascularization procedures. In the recently reported AIRE study, there was only a small difference in the rates of MI[9]. However, the median follow-up in this study was relatively short compared to SOLVD and SAVE, there was a high non-compliance rate to the treatment allocation by one year and the number of cases of MI were small. Collectively, therefore, these data indicate that in patients with low EF, ACE inhibitors prevent major ischaemic events such as myocardial infarction, unstable angina and the need for revascularization procedures (Table 2). However, these data require confirmation before ACE inhibitors are used in patients with LV dysfunction or heart failure.

Comparison of ACE inhibitors with other vasodilators

There are limited data comparing the effect of ACE inhibitors with other vasodilators. One moderately large study, the V-HeFT II, randomized patients to receive an ACE inhibitor, enalapril, or the combination of hydralazine plus isosorbide dinitrate[12]. In this trial, there was a trend toward fewer deaths in the patients treated with enalapril. However, the improvements in ejection fraction and exercise tolerance tended to favour patients receiving hydralazine plus isosorbide. In addition, contrary to the results of the other major trials, the main impact was on arrhythmic death rather than worsening heart failure. These results may be because both vasodilators may be equally effective in reducing deaths due to pump dysfunction, whereas, they may have differing effects on sympathetic activation and on sudden death. For example, hydralazine increases sympathetic activity, whereas, ACE inhibitors decrease sympathetic activity.

Vasodilators, as a class, appear to have a beneficial effect on heart failure symptoms, but ACE inhibitors have additional advantages. The most obvious beneficial effect is inhibition of the renin-angiotensin-aldosterone system. Others may include attenuation of the sympathetic nervous system and blocking the effects of various trophic factors (including angiotensin II) in the myocardium. These data indicate that the impact of a treatment on mortality and morbidity may not necessarily be reflected by the impact of the treatment on surrogate endpoints, such as ejection fraction or exercise tolerance.

Another vasodilator, flosequinan, has been shown to improve exercise tolerance when added to pre-existing triple therapy with diuretics, digoxin and ACE inhibitors. A preliminary meta-analysis of the exercise tolerance trials indicated a non-significant excess in mortality (unpublished data from FDA presentation). The recently terminated PROFILE study indicated a substantial increase in mortality with the use of flosequinan in patients with Class III and IV heart failure. Patients receiving flosequinan demonstrated an increase in heart rate, probably reflecting an increase in sympathetic activity. These data from the V-HeFT II Study and the PROFILE Study, therefore, indicate that the benefits of ACE inhibitors are not solely due to their vasodilatation effects but are probably due to their neurohormonal effects and perhaps effects on the myocardium and vascular wall.

The results from V-HeFT I provide further evidence that not all vasodilators are equally effective in heart failure[12]. Therefore, one should not assume that vasodilators, as a group, will lead to clinical benefit. Another important lesson from these studies is that the impact of treatment on surrogate end-points such as exercise tolerance or ejection fraction may be misleading and may not necessarily translate into clinically worthwhile benefit.

Subgroup effects

Subgroup analyses of the SOLVD and SAVE trials indicate that treatment was beneficial in a large number of subgroups identified. These include patients of both genders, left ventricular dysfunction of different aetiologies, and different background therapies. However, it appears that the reductions in mortality and hospitalizations for heart failure were greater in patients with more severe degrees of left ventricular dysfunction and it also appears that by comparing the results in CONSENSUS I, AIRE, the SOLVD Treatment Trial, and the SOLVD Prevention Trial, that the benefits both in terms of absolute risk reductions and rela-

Table 2 Effect of enalapril on the development of myocardial infarction, hospitalization for worsening angina, and cardiac and total mortality in the SOLVD combined trials

Outcome	No. of events (%)		Risk reduction (%) (95% CI)	Z score	*P* value
	Placebo	Enalapril			
Myocardial infarction	362 (10.6)	288 (8.5)	23 (11,34)	3·38	0·001
Hospitalization for angina*	595 (17·5)	499 (14·7)	20 (9,29)	3·61	0·001
MI or hospitalization for angina	859 (25·3)	707 (20·8)	22 (14,29)	4·89	0·0001
Cardiac deaths, nonfatal MI	918 (27·0)	758 (22·3)	21 (13,28)	4·72	0·0001
Cardiac deaths, nonfatal MI or hospitalization for angina	1350 (39·7)	1117 (32·9)	22 (16,28)	6·20	0·0001
All deaths, nonfatal MI or hospitalization for angina	1422 (41·8)	1205 (35·5)	20 (14,26)	5·82	0·0001

* The data above regarding hospitalization for angina includes both the primary or secondary discharge diagnosis. The number of patients hospitalized with a primary diagnosis of worsening angina are: prevention trial (329 placebo versus 296 enalapril, Z = 1·61) treatment trial (204 placebo versus 166 enalapril, Z = 2·55) and combined trial (533 placebo versus 462 enalapril, Z = 2·84).
MI = myocardial infarction.

tive risk reductions were greater in those with more marked symptoms.

A meta-analysis of all available trials in patients with LV dysfunction and heart failure is required to clarify the effects of ACE inhibitors in a variety of subgroups. With the recent completion of the AIRE Study with ramipril on 2000 patients, and the expected completion of the TRACE Study with Trandolapril in 1994, a total of about 14 000 patient data will become available. These data should, therefore, provide more reliable information on subgroup effects than any single trial. Such a meta-analysis is being coordinated by the ACE inhibitors Collaborative Pooling Project.

Mechanism of action of ACE inhibitors

The immediate goal of the treatment of heart failure has been the relief of symptoms. Reductions in mortality and morbidity rates are also desirable, but have been more difficult to achieve. Traditionally, the treatment of heart failure has consisted in the use of digoxin and diuretics, which in many cases effectively relieves symptoms, but there is no evidence of reduced mortality. Furthermore, diuretics and some vasodilator drugs (e.g. hydralazine) may activate the neurohormonal system. The degree of activation of the neurohormonal system in patients with heart failure correlates with higher mortality[14,15]. Drugs that increase the activity of the neurohormonal system may not be expected to reduce mortality. Furthermore, not all vasodilators have been found to reduce mortality[13].

ACE inhibitors act as vasodilators, but the most obvious potential benefit is their action to inhibit the renin-angiotensin-aldosterone system. This class of drug prevents worsening heart failure symptoms, improves NYHA functional status and exercise capacity. From a pathophysiological perspective, prolongation of survival and prevention of morbidity may be best achieved by therapies which correct the underlying abnormalities. These abnormalities include cardiac dilatation, with a tendency to progressive increase in cardiac volumes, cardiac hypertrophy, neurohormonal activation of multiple vasoconstrictor and vasodilator mechanisms[14], increased sympathetic activity and reduced parasympathetic activity, ongoing ischaemia, tendency for arrhythmic events, and haemodynamic abnormalities[11,14–18].

ACE inhibitors have been shown to prevent cardiac dilatation in patients with large anterior infarction and reduced ejection fraction, in those with asymptomatic LV dysfunction due to any cause (generally these patients were remote from an acute infarction) and in patients with overt heart failure[5,6,16]. It appears that the prevention of cardiac dilatation in patients with LV dysfunction long-term, following infarction or in heart failure, is likely to lead to benefit[5,6,16]. This benefit has been shown with a number of agents, although at the time of writing there is no clear-cut evidence that prevention of cardiac dilatation would be of benefit in an unselected group of patients with acute infarction[8]. ACE inhibitors have also been shown to reduce LV hypertrophy in patients with CHF and also improve various indices of diastolic dysfunction[17]. In several studies, ACE inhibitors have been shown to reduce the levels in angiotensin II, norepinephrine, and ANF[19]. The improvement in neurohormonal profile appears to be related to the baseline abnormality so that patients with more extensive activation of neurohormones tend to show greatest benefit. ACE inhibitors have not been shown to reduce the incidence of arrhythmias recorded on continuous 24 h Holter monitoring or clinically important non-fatal arrhythmic events, such as non-fatal cardiac arrest or sustained ventricular tachycardia[4].

In addition to the beneficial haemodynamic effects and effects on the myocardium, ACE inhibitors prevent vascular hypertrophy and, in animal models, atherosclerotic lesions[20]. Angiotensin II is known to be a powerful growth stimulant and increases the activity of second messenger RNA such as *c-myc* and *c-fos*. The proliferative effects of angiotensin II lead to increased cardiac hypertrophy, and increased smooth muscle hyperplasia in the vascular wall. Data from a variety of animal experiments indicate that ACE inhibitors have the potential of decreasing arterial 'atherosclerosis' and smooth muscle hyperplasia by a mechanism that may be mediated through the prevention of the effects of angiotensin II, by potentiation of bradykinin and by reducing the levels of aldosterone in the circulation. Whether these latter effects translate into clinical benefits is speculative and there are several ongoing trials evaluating this question.

These data, in conjunction with the mortality/morbidity results, provide a rational basis for the use of ACE inhibitors in patients with left ventricular dysfunction with or without symptoms of heart failure (Table 3). The currently recommended approach would be to include ACE inhibitors as early as possible in the treatment of these patients.

Limitations of the available data

The currently available data on ACE inhibitors are almost entirely among patients with low EF. (The recently completed study, AIRE, did not routinely measure EF). Given a tendency towards less benefit in those with lower degrees of LV dysfunction seen in the SOLVD and SAVE Trials, it would not be prudent to extrapolate the results of these trials to patients with ejection fractions over 40%. Although it appears that the anti-ischaemic effect of ACE inhibitors could potentially be extrapolated to those with

Table 3 Summary of effects of ACE inhibitors in patients with left ventricular dysfunction/heart failure

(a) Pathophysiological
1. Reduced preload and afterload.
2. Reduced cardiac dilatation and left ventricular mass.
3. Reduced levels of angiotensin II, norepinephrine, atrial natriuretic peptide, and aldosterone.
4. Antiproliferative effects on vascular tissue.
(b) Clinical
1. Improved functional capacity and reduced symptoms.
2. Prevention of heart failure.
3. Prevention of unstable angina and myocardial infarction.
4. Prevention of hospitalization for heart failure.
5. Reduced mortality.

Table 4 Long term trials of ACE inhibitors on atherosclerosis or ischaemic events in patients without heart failure or low ejection fraction

Name of trial	ACE inhibitor	Primary outcome	No. of patients	Mean duration of treatment
1. HOPE	Ramipril	Myocardial infarction + stroke + death	8000	3·5 years
2. SECURE	Ramipril	B-mode ultrasound	700	3 years
3. QUIET	Quinapril	Clinical events Angiographic substudy	1800	3 years
4. SCAT	Enalapril	Angiography	400	3 years
5. New Zealand	Ramipril	B-mode ultrasound	600	2 years

relatively preserved left ventricular function, this hypothesis requires verification in prospectively designed studies. At present, there are two large trials looking at the effects of ACE inhibitors in the prevention of ischaemic events in high risk patients without heart failure or LV dysfunction (Table 4). These include the QUIET (Quinapril Ischemic Event Trial) study, with quinapril in 1800 patients and the HOPE (Heart Outcomes Prevention and Evaluation) Study, with ramipril in 8000 patients. The collective results from these and other smaller trials examining the effects on progression of atherosclerosis (e.g. SCAT (Simvastatin Coronary Atherosclerosis Trial) with enalapril and SECURE (Study to Evaluate Carotid Ultrasound changes with Ramipril and vitamin E) and PART (Prevention of Atherosclerosis with Ramipril Therapy) with ramipril should provide useful information regarding both the clinical impact of such therapy in preventing myocardial infarction and other ischaemic events and progression of vascular lesions.

We thank Grace Chaves for secretarial support.

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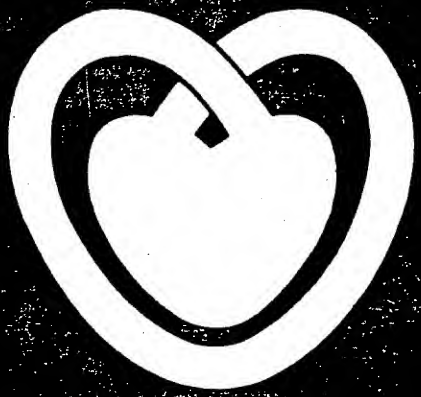
The role of converting enzyme inhibition in patients after acute myocardial infarction



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Current Perspectives

Emerging Role of Angiotensin-Converting Enzyme Inhibitors in Cardiac and Vascular Protection

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Angiotensin-converting enzyme (ACE) inhibitors are commonly used drugs in the management of a variety of cardiovascular diseases. They are effective antihypertensive agents.[1-3] Early studies have demonstrated reductions in mortality and symptoms of heart failure in patients with severe congestive heart failure.[4] More recently, clinical trials have demonstrated reductions in mortality and in hospitalizations for heart failure when these agents were used in patients with moderate left ventricular dysfunction, with and without overt heart failure, further expanding the clinical value of these drugs in the management of patients with cardiac diseases. These benefits have been observed consistently in several trials,[5-7] in patients with ischemic and nonischemic causes for the left ventricular dysfunction and with or without recent myocardial infarction. The reductions in progressive heart failure and mortality in these patients are at least partly related to a beneficial effect on left ventricular remodeling and reductions in left ventricular enlargement.[8-10] Other potential beneficial effects of these agents, such as regression of left ventricular hypertrophy and retardation of the rate of loss of renal function in patients with diabetic nephropathy, have been brought into focus by recent trials and also by experimental studies that explore their mechanisms of action.

A new and important potential role for ACE inhibitors is suggested by the recent trials in patients with low ejection fraction, which documented a significant reduction in major ischemic events such as myocardial infarction, unstable angina, and the need for coronary revascularization procedures. In addition, parallel epidemiological, genetic, and experimental studies suggest that the renin-angiotensin-aldosterone system may have a role in the development of coronary artery disease and its clinical sequelae not only in patients with left ventricular dysfunction or overt heart failure but also in other high-risk patients.

This article will summarize several independent and complementary lines of evidence suggesting that ACE inhibitors may reduce the risk of ischemic events in patients at high risk of developing major vascular events.

Biological Rationale for the Cardioprotective Effects of ACE Inhibitors in Preventing Myocardial Ischemia and Infarction

The renin-angiotensin-aldosterone system is complex and acts as a circulating hormonal system, a local endogenous tissue hormonal system with autocrine and paracrine effects, and a neurotransmitter and neuromodulator. Current experimental evidence suggests that ACE inhibitors reduce the risk associated with atherosclerotic cardiovascular disease through multiple mechanisms (Table 1). These can be classified into "cardioprotective" effects, referring to the benefits in overall cardiac hemodynamics, energetics, electrical stability, and the reduction in left ventricular mass, and "vasculoprotective" effects, related to direct antiproliferative effects, possible antiatherogenic properties, and favorable effects on thrombotic mechanisms and on arterial compliance and tone. ACE inhibitors probably exert these protective effects by blocking both circulating and tissue renin-angiotensin systems.

The cardioprotective effects of ACE inhibitors are well documented[11] (Table 1) and can be summarized as follows.

Restoring the Balance Between Oxygen Supply and Demand

Angiotensin II is a potent direct systemic and coronary vasoconstrictor that increases myocardial inotropy by its ability to raise the cytosolic Ca^{2+} concentration in the myocardium[11-16] and therefore adversely affects the balance between myocardial oxygen supply and demand. Gavras and Gavras[17] reported that infusion of angiotensin II in rabbits resulted in myocardial infarction. Inhibition of the enzyme that converts angiotensin I to angiotensin II reduces the loading conditions of the heart (by reducing preload and afterload), thereby decreasing ventricular wall stress. ACE inhibitors also reduce left ventricular dilatation by reducing early infarct expansion and ventricular remodeling after experimental[18] and human infarction.[8-10] This reduction in

Received March 30, 1994; revision accepted June 10, 1994.

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TABLE 1. Cardioprotective and Vasculoprotective Effects of Angiotensin-Converting Enzyme Inhibitors

Cardioprotective effects
Restoring the balance between myocardial oxygen supply and demand
Reduction in left ventricular preload and afterload
Reduction in left ventricular mass
Reduction in sympathetic stimulation
Beneficial effect on reperfusion injury*
Vasculoprotective effects
Direct antiatherogenic effect*
Antiproliferative and antimigratory effects on smooth muscle cells, neutrophils and mononuclear cells
Improvement and/or restoration of endothelial function
Protection from plaque rupture*
Antiplatelet effects
Enhancement of endogenous fibrinolysis*
Antihypertensive effects
Improvement in arterial compliance and tone

*Not demonstrated conclusively in humans.

ventricular dilatation also reduces wall stress and thus myocardial oxygen demand. Blockade of angiotensin II–mediated coronary vasoconstriction and the resulting increase in coronary blood flow, demonstrated in animals and in human subjects,[19-28] contribute to increased oxygen supply. The net effect of these actions is a decrease in myocardial oxygen demand and an increase in myocardial oxygen supply. This beneficial effect is maintained by the absence of reflex tachycardia, which may occur with other vasodilators. Improved cardiac hemodynamics and improved energy supply to the myocardium have been demonstrated in human subjects treated with ACE inhibitors in the setting of acute and chronic heart failure and acute and chronic myocardial ischemic damage.[29-34] ACE inhibitors also cause regression of left ventricular hypertrophy with an associated improvement in ventricular relaxation (see below). They also increase arterial compliance.[35] These are important mechanisms of improving the balance of myocardial oxygen supply and demand and coronary reserve in patients with left ventricular hypertrophy, such as those with hypertensive heart disease, but also those with compensatory hypertrophy after myocardial infarction.[36]

Reduction in Left Ventricular Mass

Increased left ventricular mass has been identified as an independent risk factor for coronary heart disease in general and is associated with increased cardiac mortality and morbidity.[37-39] While left ventricular hypertrophy occurs primarily in hypertensive individuals, the Framingham Heart Study suggested an association between left ventricular mass and cardiovascular mortality in the general population.[40] ACE inhibitors have been consistently shown to be effective in reducing left ventricular mass in animal models and in hypertensive subjects.[41-46] Prevention and regression of ventricular hypertrophy is related in part to reduced afterload, inhibition of myocardial smooth muscle cell hypertrophy,[11] and restructuring of the elastic and collagen fibers of the myocardium, limiting the remodeling process.[47,48] Recent experimental evidence[49] suggests that load-independent mechanism(s) could also play a role in regression of left ventricular mass with ACE inhibitor therapy. For example, rats with left ventricular hypertrophy produced by banding of the abdominal aorta, when treated with the high-affinity binding ACE inhibitor ramipril, exhibited a reduction in left ventricular mass, even when the drug was used in doses too low to reduce blood pressure. These findings were attributed to a direct inhibition of cardiac tissue ACE, resulting in blockade of the angiotensin II–mediated myocyte hypertrophy. Both circulating and locally (cardiac) produced angiotensin II appear to affect cardiac growth, although the precise contributions of these two sources of angiotensin II are not yet entirely clear. Proof for the direct involvement of angiotensin II in the development of cardiac hypertrophy is strengthened by recent experimental studies in spontaneously hypertensive rats with marked cardiac hypertrophy in which both renin and angiotensinogen mRNA are increased in the myocardium compared with that in normotensive rats.[50] Similarly, angiotensinogen gene expression is also transiently increased in the hypertrophied region of the left ventricular myocardium after coronary occlusion.[51,52] Therefore, angiotensin II contributes to an increase in left ventricular mass by directly promoting myocyte growth as well as by stimulating vascular smooth muscle cell growth and proliferation (see below). Aldosterone may also contribute to an increase in left ventricular mass[53,54] by increasing myocardial collagen content.[54] The combined effect of activation of the renin-angiotensin-aldosterone system is therefore an increase in left ventricular mass related to cardiac myocyte hypertrophy, increase in the mass of the extracellular collagen matrix, and hypertrophy of vessel walls. Production of both angiotensin II and aldosterone is inhibited by ACE inhibitors, resulting in reductions in left ventricular mass.

While extensive and consistent evidence is available showing the efficacy of ACE inhibitors in reducing left ventricular mass in humans, a clear reduction in cardiovascular events associated with this effect is not yet clearly established. Early findings regarding the mechanisms involved in ACE inhibitor–mediated reduction in left ventricular mass are based largely on experimental work in animal models and cell cultures and require further confirmation including assessment of how relevant they are in human subjects, since the distribution of ACE in cardiac tissue and vascular wall is known to be subject to great interspecies variability.

Neurohormonal Effects

Angiotensin II activates both the central and the peripheral sympathetic nervous systems.[55-59] It is an important regulator of noradrenaline release from sympathetic nerve terminals by its action on prejunctional receptors, and it may therefore modulate local cardiac and vascular sympathetic activity.[60,61] Inhibition of this effect of angiotensin II could also potentially account for a reduction in cardiovascular ischemic events. Caution is suggested in the interpretation of the results of these experimental studies, since the importance of this mechanism in humans is not entirely clear. Data in

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humans are conflicting: one recent small study by Goldsmith et al[62] suggests that in patients with compensated congestive heart failure, ACE inhibitor therapy might not significantly affect plasma noradrenaline or systemic venous norepinephrine spillover, whereas data from the Studies of Left Ventricular Dysfunction (SOLVD) indicate a significant drop in plasma norepinephrine that is most marked in patients with initially greater elevations of plasma norepinephrine.[63] Similarly, Gilbert and coworkers[64] found that lisinopril lowered cardiac adrenergic drive and increased β-receptor density in subjects with heart failure with increased cardiac adrenergic drive, suggesting that cardiac antiadrenergic properties contribute to the efficacy of ACE inhibitors in subjects with heart failure. The importance of the antiadrenergic properties of ACE inhibitors in humans in the absence of heart failure is even less clear.

Other Effects

Other potential cardioprotective actions of ACE inhibitors in acute ischemia are suggested primarily by experimental studies in animals and include a reduction in infarct size in some but not all studies,[65-72] a beneficial effect on reperfusion injury including improvement of contractility of the stunned myocardium,[65,70,71] reduction in reperfusion arrhythmias and the potential to reduce other ventricular arrhythmias,[73-75] and possibly (still controversial) beneficial effects related to an antioxidant (free scavenger) action.[76,77] These effects have been studied primarily in experimental animal preparations. Their importance in acute ischemic syndromes in human subjects remains unclear.

The vascular protective effects (Table 1) of ACE inhibitors have recently received considerable attention and can be summarized as follows.

Direct "Antiatherogenic" Effect

A direct "antiatherogenic" action of these drugs has been shown in several animal models of atherosclerosis related to cholesterol-mediated endothelial injury[78-81] and in models of accelerated atherosclerosis after mechanical endothelial damage (balloon endothelial injury)[82,83] or immune mechanism–mediated endothelial damage (allograft vasculopathy).[84] The direct "antiatherogenic" action of ACE inhibitors observed in these experiments is related to complex effects mediated by these agents, including an antiproliferative and antimitogenic action, beneficial effects on endothelial function, possible plaque-stabilizing effects, antithrombotic effects, the action of these agents on the sympathetic nervous system, and possible antioxidant properties.

Chobanian and coworkers[78,79] studied the effects of captopril in the normotensive Watanabe heritable hyperlipidemic (WHHL) rabbit, an experimental model in which other blood pressure–lowering drugs such as propranolol, nifedipine, and verapamil failed to inhibit the development of atherosclerotic lesions. Captopril reduced the total aortic intimal surface covered with atherosclerotic lesions and decreased the cellularity and cholesterol content of atherosclerotic plaques and increased their extracellular matrix. It appears, therefore, that in addition to a reduction in the anatomic extent of atherosclerotic lesions, captopril had potentially stabilizing effects on the atherosclerotic lesions, which may be associated with less propensity to rupture. Similar results were reported by Aberg and Ferrier[80] in the cholesterol-fed cynomolgus monkey model of atherosclerosis. Rolland and coworkers[81] demonstrated a reduction in the atherosclerotic lesion size, a decrease in the lipid-laden macrophages, and less fragmentation of the arterial elastic tissue in the Pitman-Moore minipig treated with the ACE inhibitor perindopril and receiving a high-fat diet. The atherosclerotic lesions that developed in perindopril-treated animals appeared more "stable" (less prone to rupture) and had improved viscoelastic properties, favoring improved arterial flow.

While these experiments are important and suggest potential benefits for the use of ACE inhibitors in ischemic cardiovascular diseases beyond their hemodynamic effects, these findings should be interpreted cautiously. The plaques produced in animals receiving high-cholesterol or high-fat diets are likely to differ from those observed in human atherosclerosis. The clinical impact of the potential to stabilize the plaque remains unclear, and direct proof that ACE inhibitors can retard the progression of atherosclerosis in humans is not available.

Powell and coworkers[82] demonstrated that administration of the ACE inhibitor cilazapril prevented myointimal proliferation and preserved lumen integrity in carotid arteries of normotensive rats after endothelial denudation by balloon injury. Similar effects have also been reported in the atherosclerotic rabbit iliac model.[83] Increases in the messenger RNA for ACE and angiotensinogen have been demonstrated in the proliferating tissue of balloon-injured vessels in rats.[85] However, important interspecies differences exist in the distribution of ACE in the arterial wall, and some investigators reported no benefit or only modest effects associated with the use of ACE inhibitors in other animal models of restenosis.[86-88] Furthermore, in two recent clinical trials, cilazapril had no effect on the incidence of restenosis after balloon angioplasty in humans.[89,90] Differences in the timing and dosage of cilazapril in these trials compared with the studies in the rat model reported by Powell et al could be important, and further studies appear warranted.

Antiproliferative and Antimigratory Effects

Data from both in vitro and in vivo studies[91-97] show that angiotensin II can produce vascular smooth muscle cell growth and proliferation, a mechanism important in the genesis and progression of atherosclerotic lesions. In animal models, angiotensin II acts by the induction of proto-oncogenes c-*fos*,[98-100] c-*myc*,[97,101] and c-*jun*[102,103] and induces the expression of several growth factor genes, such as the genes encoding for the α-chain of platelet-derived growth factor, transforming growth factor-β, and thrombospondin.[97,104-106] Early activation of these proto-oncogenes followed by sequential activation of growth factor genes (and possibly other genes involved in cell growth) ultimately result in vascular smooth muscle cell growth. In addition to the trophic effect on vascular smooth muscle cells, angiotensin II has been shown to release an endothelial neutrophil chemoattractant (which is as yet unidentified), leading to neutrophil accumulation.[107] Recent experiments in spontaneously hypertensive rats demonstrated decreased subendothelial accumulation of mononuclear macrophages after treatment with cilazapril.[108,109] These

cells are all involved in the development of atherosclerotic lesions, and by decreasing their migration, ACE inhibitors could prevent lesion formation.[110] In contrast to these antiproliferative and antimigratory effects, an enhancement of endothelial cell migration has been demonstrated with ACE inhibitors and decreases in angiotensin II that may contribute to improved endothelial function and might therefore exert an antiatherosclerotic action.[111]

Improvement and/or Restoration of Endothelial Function

ACE inhibitors have been shown to improve or restore endothelial function in different animal models such as the spontaneously hypertensive rat,[109] the hypercholesterolemic rabbit,[112] in other normotensive animals,[113] and in experimental heart failure models.[114] This effect of ACE inhibitors appears to be mediated primarily by bradykinin accumulation. Since ACE is identical to the kininase II of the kallikrein-kinin system that inactivates bradykinin,[115] it leads to the accumulation of kinins (potentiation of bradykinin effects). Bradykinin has a direct vasodilator effect and acts also by release of the potent arteriolar dilator nitric oxide (NO or endothelium-derived relaxing factor [EDRF]) and prostacyclin (PGI_2) from endothelial cells (complex interactions with the prostaglandin system). EDRF is a potent coronary vasodilator and has other beneficial effects on endothelial function and integrity: it inhibits platelet adhesion and aggregation, smooth muscle cell mitogenesis, and proliferation and could thereby play an important role in preventing the development of proliferative atherosclerotic lesions in response to vascular injury.[116] Bradykinin may also cause vasodilatation by interfering with eicosanoid metabolism and by increasing synthesis of a vasodilator prostanoid.[117] Improved endothelial function and vascular reactivity could also be mediated by inhibition of the angiotensin II stimulation of endothelial production of endothelin.[118]

Aldosterone may also be implicated in endothelial dysfunction, as evidenced by studies in patients with primary aldosteronism and correction of the endothelial function abnormalities after removal of the aldosterone-producing tumor.[119] The relevance of these observations to other patients is unclear, since aldosterone levels are considerably increased in the presence of aldosterone-producing tumors and similar levels of aldosterone increase have generally not been measured in patients after myocardial infarction, heart failure, and other ischemic syndromes.

Protection From Plaque Rupture

ACE inhibitors may also play a role in reducing the propensity for plaque rupture by several mechanisms. We discussed earlier the morphological changes in plaques associated with the use of ACE inhibitors in animal models of atherosclerosis and how these changes could potentially contribute to "plaque stabilization." Other mechanisms of preventing plaque rupture may be mediated through direct inhibition of angiotensin II–mediated vasoconstriction, effects on endothelin or on serum and tissue magnesium: Angiotensin II stimulates release of endothelin. Endothelin is one of the most potent coronary vasoconstrictors, and its local release might, in the presence of a susceptible atherosclerotic lesion, accelerate plaque rupture.[118,120] Inhibition of angiotensin II could potentially block this effect. Hypomagnesemia has been shown to cause an increase in coronary vascular reactivity[121] and could potentially accelerate plaque rupture. Individuals living in areas with low magnesium levels have been shown to have a high incidence of myocardial infarction, and experimental hypomagnesemia has led to coronary artery spasm.[122] ACE inhibitors increase serum and tissue magnesium and could therefore have beneficial effects.

Definitive proof that ACE inhibitors provide protection from plaque rupture is not yet available.

Antithrombotic Effects

Recent evidence suggests that ACE inhibitors can also affect arterial thrombosis by effects on platelets and on the endogenous fibrinolytic system. Several investigators[123,124] have demonstrated that captopril inhibits platelet aggregation. This reduces the release of vasoconstrictors (such as thromboxane A_2) from platelets and of stimulators of smooth muscle cell proliferation (such as platelet-derived growth factor). It has been demonstrated that human platelets possess angiotensin II receptors. The action of ACE inhibitors on the platelets could be related to angiotensin II blockade. Platelet aggregation may also be suppressed through increased prostacyclin and EDRF, induced by elevated bradykinin levels, as well as by an increase in serum magnesium.

In vitro studies have demonstrated that angiotensin II selectively induces the production and secretion of plasminogen activator inhibitor-1 (PAI-1) in endothelial cells[125] and in cultured astrocytes.[126] PAI-1 is the most important physiological inhibitor of tissue-type plasminogen activator (TPA) in plasma,[127] and elevated levels have been implicated in the pathogenesis of thromboembolic disease.[128] A recent small investigation in human subjects demonstrated a rapid and significant increase in PAI-1 after the infusion of angiotensin II.[129] This effect appeared to be dose related and occurred in both normotensive and hypertensive subjects. These findings suggest that angiotensin II may be prothrombotic at least in part by increasing plasma levels of PAI-1, thereby reducing the activity of the fibrinolytic system. An important action of ACE inhibitors may be to improve endogenous fibrinolytic function among patients at high risk for ischemic events. These early observations, which are derived from a small number of individuals tested, require further confirmation in larger studies and suggest a potentially important link between the renin-angiotensin system and risk for thrombosis.

Antihypertensive Effects

The antihypertensive action of ACE inhibitors by itself is likely to contribute to their ability to reduce coronary heart disease and strokes. The link between hypertension and atherosclerosis is well established.[130] Epidemiological studies demonstrate that elevations in blood pressure levels are associated with increased risk of coronary artery disease and that this risk is "continuous," even within ranges considered to be "normotensive."[131] Antihypertensive therapy has been shown to reduce the anatomic extent of atherosclerosis,[130] the risk of stroke, and to a lesser extent, the risk of coronary heart disease.[132] ACE inhibitors are effective blood

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pressure–lowering agents[1-3] and have no adverse metabolic effects on lipids and blood glucose levels.[133-137] Therefore, it is theoretically possible that ACE inhibitors could reduce the risk of coronary heart disease to a greater extent than that seen with moderate to high doses of diuretics (which have been extensively evaluated) because of the lack of adverse metabolic effects and their special "antiatherosclerotic" properties. This hypothesis remains unproven, however, and is currently being evaluated in large randomized trials. The results of the SOLVD and of the Survival and Ventricular Enlargement Trial (SAVE) (see below), as well as the antiatherogenic effect of ACE inhibitors in the normotensive animal models of atherosclerosis, however, suggest that a reduction in major ischemic events may be expected to occur with ACE inhibitor therapy and that the magnitude of benefit may be larger than that expected purely from a blood pressure–lowering effect. Therefore, it is likely that other mechanisms of action may also be relevant.

Epidemiological and Genetic Studies: Link Between the Renin-Angiotensin System and the Risk for Myocardial Infarction

Several epidemiological studies have examined the relation between plasma renin levels in hypertensive patients and the risk for ischemic events. Early studies reported conflicting results,[138,139] and conclusions from these investigations are limited by methodological shortcomings, such as selection bias, retrospective analysis, and differences in the laboratory assays used for measuring plasma renin activity. The best epidemiological evidence for an association between plasma renin levels and the risk for subsequent myocardial infarction is provided by a recent prospective cohort study, in which Alderman and coworkers[140] report findings in 1717 subjects with mild and moderate hypertension followed for a mean of 8.3 years. The risk of myocardial infarction was increased 5.3-fold among subjects with high versus those with low renin profiles (95% CI, 3.4 to 8.3), and this effect was independent of other established cardiovascular risk factors, such as age, sex, race, smoking status, cholesterol and glucose levels, and systolic and diastolic blood pressure levels. This association between elevated renin levels and myocardial infarction may be causal or secondary to preexisting underlying cardiovascular disease resulting in an activated renin-angiotensin system.[141] Moreover, it is not clear whether these observations are generalizable to individuals without high blood pressure. A recent prospective study by Meade et al[142] failed to demonstrate an independent association between plasma renin levels and the risk for myocardial infarction in normotensive individuals. This study does not necessarily contradict the findings by Alderman et al, since among men whose systolic blood pressures were in the highest third of the distribution, there may have been an association between plasma renin activity and subsequent coronary events.

Cambien and coworkers[143] have recently reported that the ACE-DD genotype, which identifies individuals with higher levels of circulating ACE, was more prevalent in middle-aged men with previous myocardial infarction (n=610) than in a case-matched control group (n=733; $P=.007$), raising the interesting possibility of ACE as a genetic predictor of coronary disease and its sequelae. The ACE-DD genotype appeared to be an independent risk factor for myocardial infarction after adjustment for the presence of other known coronary risk factors such as smoking, dyslipidemia, and hypertension. It is of particular interest that, although for the entire study population the ACE-DD genotype was associated with only a modest increase in the risk for myocardial infarction (odds ratio of 1.34), in a subgroup analysis of patients without other risk factors, the risk of myocardial infarction was increased more markedly (odds ratio of 3.2). Therefore, it appears that patients who are homozygous for the deletion polymorphism represent a group at considerably increased risk for myocardial infarction, even in the absence of other risk factors. While this observation awaits further confirmation, it may provide us with clues as to why certain individuals with no or very few conventional risk factors for coronary artery disease develop myocardial infarction. It also supports a role for the renin-angiotensin system in the pathogenesis of coronary artery disease and its complications. The same group of investigators also demonstrated an excess of both ACE-DD (odds ratio, 2.6; $P=.02$) and ACE-ID (odds ratio, 1.9; $P=.08$) genotypes among individuals with a parental history of myocardial infarction compared with age-matched controls.[144]

The ACE-DD genotype has also been associated with hypertrophic cardiomyopathy and with sudden death in families with this disease,[145] and a recent study showed an increased frequency of this genotype in patients undergoing cardiac transplantation for ischemic or idiopathic dilated cardiomyopathy.[146]

These studies suggest a link between activation of the renin-angiotensin system and increased cardiac hypertrophy, vascular hypertrophy, and atheroma development and rupture. Consequently, ACE inhibitors could potentially reduce myocardial ischemic events.

Evidence From Randomized Clinical Trials

The role of ACE inhibitors in preventing the clinical sequelae of atherosclerotic cardiac disease has been evaluated in various patient populations: those with reduced left ventricular ejection fraction, with and without recent myocardial infarction, in the acute phase of myocardial infarction, after coronary angioplasty, and with chronic stable angina.

Long-term Trials in Patients With Heart Failure and Low Ejection Fraction

Three recent large randomized trials in patients with low left ventricular ejection fraction followed over a period of >3 years reported significant reductions in myocardial infarction with the use of ACE inhibitors: The SOLVD trials included patients with left ventricular ejection fraction of ≤0.35. Patients with congestive heart failure entered the Treatment Trial,[5] and those without overt heart failure and receiving no therapy for heart failure entered the Prevention Trial.[6] Patients in both trials had not sustained a recent myocardial infarction in the month before enrollment, nor did they have unstable angina or any clear indications for revascularization at study entry. The SAVE trial[7] enrolled patients within 3 to 16 days after myocardial infarction

TABLE 2. Characteristics of Large Randomized Studies of Angiotensin-Converting Enzyme Inhibitors in Patients With Low Ejection Fractions

	SOLVD Treatment Trial	SOLVD Prevention Trial	SAVE	AIRE
Sample size	2569	4228	2231	2006
Design	Prospective double-blind	Prospective double-blind	Prospective double-blind	Prospective double-blind
ACE inhibitor used	Enalapril	Enalapril	Captopril	Ramipril
Patient population*				
Mean age, y	60.8	59.1	59.4	64.9
Sex ratio, M/F, %	80.4/19.6	88.6/11.4	82.5/17.5	74/26
Recent MI	No	No	Yes	Yes
Mean LVEF, %	25	28	31	Not available
LVEF inclusion threshold, %	<35	<35	<40	Not available
Symptomatic heart failure	Yes	No	No	Yes
Ischemic heart disease, %	71.1	83.2	100	100
Duration of follow-up, mo	41.4	37.4	42	15

SOLVD indicates Studies of Left Ventricular Dysfunction; SAVE, Study of Survival and Ventricular Enlargement; AIRE, The Acute Infarction Ramipril Efficacy Study; ACE, angiotensin-converting enzyme; MI, myocardial infarction; and LVEF, left ventricular ejection fraction.

*All relevant clinical patient characteristics were similar in the placebo and treatment groups.

with left ventricular ejection fraction of ≤0.40 who were asymptomatic or had only mild heart failure. Patients underwent revascularization procedures before study entry if they had objective evidence of ischemia. In all these three trials, mean duration of treatment was close to or exceeding 40 months. The prolonged duration of treatment is probably essential for the anti-ischemic action of ACE inhibitors to become manifest. Key study characteristics of these trials (and of the Acute Infarction Ramipril Efficacy [AIRE] Study[147] [see below]) are summarized in Table 2. The main end points in the SOLVD and SAVE trials was mortality. Development of myocardial infarction was a predefined secondary end point in these studies, and data on myocardial infarction were therefore prospectively and systematically collected. A significant risk reduction (RR) in the incidence of myocardial infarction was observed in each of these three long-term trials, and all were of similar

TABLE 3. Effect of ACE Inhibitors on Myocardial Infarction and on Unstable Angina in Patients With Low Ejection Fraction

	MI Incidence, No. (%)				Unstable Angina, No. (%)			
Trial	ACE-I	Placebo	Risk Reduction, % (95% CI)	*P*	ACE-I	Placebo	Risk Reduction, No. (%) (95% CI)	*P*
SOLVD* Treatment Trial	127 (9.9)	158 (12.3)	23 (2, 39)	.02	187 (14.6)	240 (18.7)	27 (12, 40)	.001
SOLVD* Prevention Trial	161 (7.6)	204 (9.1)	24 (6, 38)	.01	312 (14.8)	355 (16.8)	14 (0, 26)	.05
SAVE†	133 (11.9)	170 (15.2)	25 (5, 40)	.015	135 (12.1)	133 (11.9)	0 (−26, 22)	.93
AIRE‡	81 (8.0)	88 (8.9)	11 (−22, 35)	NS	Not available	Not available	Not available	...
Combined Trials§ (N=11,034)	502 (9.1)	620 (11.3)	21 (11, 30)‖	<.002	634 (14.1)	720 (15.9)	15 (4, 24)	<.003

ACE indicates angiotensin-converting enzyme; MI, myocardial infarction; and ACE-I, ACE inhibitor.

*Clinical diagnosis by treating physician of MI confirmed in 94% of patients as having two or three documented classic criteria of characteristic chest pain, typical electrocardiographic changes, and typical enzyme changes or fatal MI documented on death certificates. Unstable angina was defined as new-onset or worsening angina pectoris requiring hospital admission.

†According to the original protocol criteria (clinically defined MI with predefined typical changes in creatine kinase levels or fatal MI validated by the Mortality Classification Committee), there were 129 cases of recurrent MI in the placebo vs 108 cases in the captopril group. This difference, although it did not reach statistical significance (risk reduction, 19%; 95% CI, −4% to 37%; *P*=.102), is similar to the results summarized in the table using clinical criteria for recurrent MI by clinic physicians.

‡Classical clinical criteria were used for defining recurrent MI. All cases presented in the final analysis were validated by a subcommittee of the International Steering Committee.

‖Derived from odds ratio calculated by the Mantel-Haenszel method.

§When the results of the SOLVD and SAVE trials only were combined (trials of long-term ACE-I therapy), the risk reduction in MI rates was 23% (95% CI, 12% to 33%); *P*<.001.

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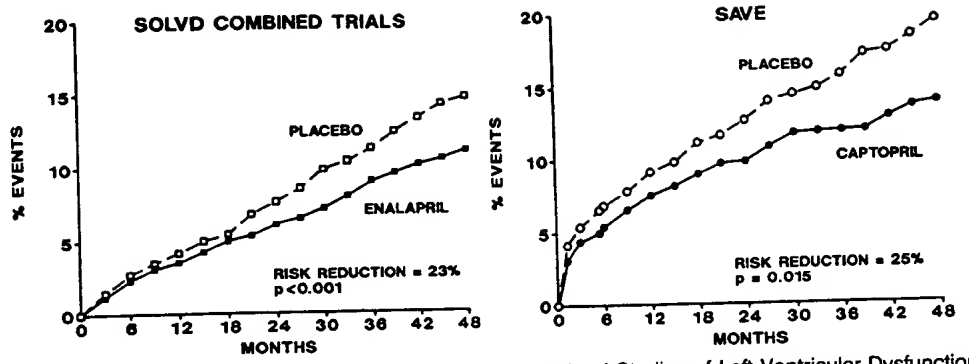

Graphs showing cumulative incidence of myocardial infarction in the combined Studies of Left Ventricular Dysfunction (SOLVD) and incidence of recurrent myocardial infarction in the Survival and Ventricular Enlargement Trial (SAVE). In both studies, differences in the incidence of myocardial infarction between ACE inhibitor– and placebo-treated patients started to become apparent after 6 months of therapy and continued to widen thereafter. (Adapted with permission from *The Lancet* and *The New England Journal of Medicine*.)

magnitude (Table 3). For the combined SOLVD and SAVE trials, a highly significant reduction in the risk for myocardial infarction is calculated (Table 3; results of the trials are combined by the Mantel-Haenszel procedure[148]). There were 421 cases of myocardial infarction in the ACE inhibitor–treated patients versus 532 cases of acute myocardial infarction in patients randomized to placebo (RR, 23%; 95% CI, 12% to 33%; $P<.001$). Furthermore, hospitalizations for unstable angina pectoris were significantly reduced in the SOLVD trials (Table 3). There were 187 hospitalizations for unstable angina in enalapril-treated patients in the SOLVD Treatment Trial versus 240 in patients allocated to placebo (RR, 27%; 95% CI, 12 to 40%; $P=.001$). In the Prevention Trial, there were 312 hospitalizations for unstable angina in the enalapril-treated patients versus 355 in patients allocated to placebo (RR, 14%; 95% CI, 0 to 26%; $P=.05$). Overall, combining both arms of the SOLVD trials, 499 (14.7%) patients in the enalapril group were hospitalized for unstable angina compared with 595 (17.5%) in the enalapril group (RR, 20%; 95% CI, 9 to 29%; $P=.001$). In the SAVE trial, the number of hospitalizations was similar in the captopril group: 135 of 1115 patients (12.1%) and in the placebo group: 133 of 1116 patients (11.9%).[149] Combining the results of the SOLVD and the SAVE trials, the risk for hospitalization for unstable angina was reduced significantly in patients treated with ACE inhibitors (RR, 15%; 95% CI, 4, 24; $P<.003$). There was also a 24% risk reduction ($P<.001$) in the need for revascularization procedures (coronary artery bypass surgery [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) in patients treated with captopril in the SAVE trial.[149]

The consistency of the impact of enalapril was examined in a number of subgroups in SOLVD.[150] Reductions in major acute ischemic events were observed in the SOLVD trials among various subgroups defined by age, sex, degree of left ventricular dysfunction (different left ventricular ejection fractions), pathogenesis of left ventricular dysfunction (ischemic versus nonischemic), with and without a history of diabetes, and against a background of different drugs (β-blockers, aspirin, calcium channel blockers). Furthermore, reductions in ischemic events were observed both among patients with overt congestive heart failure, who probably had elevations in plasma renin levels, and in patients without heart failure, who presumably did not have elevated plasma renin levels in the absence of diuretic therapy.[151] In addition, the observed reduction in ischemic events cannot be explained by the hypotensive actions of ACE inhibitors alone, since the magnitude of risk reduction was substantially larger than that expected from short-term, modest reductions in blood pressure. In a recent meta-analysis of 14 randomized clinical trials of antihypertensive therapy, diastolic blood pressure reductions of 5 to 6 mm Hg for about 4 to 5 years resulted in a 14% reduction in fatal and nonfatal coronary heart disease events.[132] In the combined SOLVD trials, diastolic blood pressure was reduced by an average of 4 mm Hg, and this was associated with a 23% reduction in fatal or nonfatal myocardial infarctions and a 21% reduction in cardiac deaths. Moreover, the risk reductions in ischemic events were similar in patients with different levels of systolic and diastolic blood pressure at baseline. There was a trend toward larger reductions in myocardial infarction and unstable angina among those with a greater reduction in blood pressures; however, these differences did not reach statistical significance. These considerations suggest that the reduction in major ischemic events observed with ACE inhibitor therapy is at least in part due to mechanisms unrelated to the hypotensive effects of these agents.

Analysis of the time course of this observed reduction in ischemic end points may also provide insights into potential mechanisms of action of ACE inhibitors. Both arms of the SOLVD trials, as well as the SAVE trial, found little difference in the incidence of myocardial infarction during the first 6 months after randomization (Figure). Differences were apparent after 6 months of treatment and continued to widen thereafter. A very similar time course of events was noted in the SOLVD trials for hospitalizations for unstable angina. This delay in the reduction of ischemic events resembles the "lag" observed in trials of cholesterol lowering and suggests that the mechanism for this observed anti-ischemic action of ACE inhibitors is unlikely to be related solely to the beneficial hemodynamic effect of the drug, which is observed immediately and which is not expected to increase with time. These observations suggest that ACE inhibitors decrease the incidence of ischemic events, which may be related to multiple mechanisms, including the prevention of the progression of coronary atherosclerosis and/or stabilization of atherosclerotic plaques. Although hemodynamic changes alone are

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unlikely to explain the anti-ischemic action of ACE inhibitors, it is possible that the continued reduction in myocardial oxygen consumption related to the effects of these drugs on afterload, preload, left ventricular geometry, and ventricular mass, possibly in conjunction with direct vascular protective effects, leads to reductions in myocardial infarction and unstable angina.

The recent AIRE study[147] randomized 2006 patients within 3 to 10 days after acute myocardial infarction who exhibited transient or persistent symptoms or signs of heart failure to treatment with the ACE inhibitor ramipril or to placebo. Patients were followed for an average of 15 months (minimum duration of follow-up was 6 months). A highly significant and substantial reduction in all-cause mortality, the primary study end point, was demonstrated (RR, 27%; 95% CI, 11% to 40%; $P=.002$), and this benefit was apparent earlier and reached statistical significance after a much shorter duration of follow-up than in the SAVE trial. Reinfarction rates were recorded prospectively. While a trend toward fewer acute myocardial infarcts was noted in patients treated with ramipril, this was not statistically significant: there were 81 recurrent infarcts (8%) in ramipril-treated patients versus 88 (9%) in patients allocated to placebo. These results do not necessarily contradict the results of the SOLVD and SAVE trials. The number of validated recurrent myocardial infarcts in the AIRE study was relatively small, largely due to the much shorter average follow-up period. The favorable trends observed are consistent with the observations made after a similar duration of follow-up in the SOLVD and SAVE trials. Even though the duration of treatment and follow-up in the AIRE study is relatively short, if these results are combined with the SOLVD and SAVE trials, the reduction in myocardial infarction risk still remains highly significant (Table 3).

Other randomized clinical trials in patients with reduced left ventricular ejection fraction contribute only little information regarding the effects of ACE inhibitors on ischemic events because of the small number of patients randomized and the short duration of follow-up. The Collaborative Group on ACE Inhibitor Trials reported a summary of 35 clinical trials of ACE inhibitors in patients with chronic heart failure and/or left ventricular dysfunction (R. Garg, S. Yusuf, personal communication). Trials other than the SOLVD trials were small and of short duration (generally only for 3 to 6 months). Overall, a significant reduction in the incidence of myocardial infarction was noted, but most end points were derived from the SOLVD trials (RR, 19%; 95% CI, 0% to 35%). In trials other than SOLVD, 2023 patients were randomized to receive an ACE inhibitor and 1568 to the control group. There were 26 myocardial infarcts in the ACE inhibitor–treated group (1.3%) versus 24 in the control group (1.5%). The evidence provided by the SOLVD and SAVE trials suggests the intriguing possibility that the reduction in ischemic events may occur in a broader group of high-risk patients such as those with preserved left ventricular ejection fraction. However, such patients may not have significant increases in the systemic levels of renin[152] and angiotensin, although activation of the local tissue angiotensin system may occur in response to atherosclerotic vascular injury. It is important, therefore, to provide direct proof of potential benefits of ACE inhibitors in such patients.

Trials in Acute Myocardial Infarction

The CONSENSUS II trial[153] randomized 6090 patients with acute myocardial infarction presenting within 24 hours of onset of symptoms to treatment with enalapril intravenously followed by oral therapy administered for 6 months versus placebo. No benefit was noted with regard to mortality (6-month mortality was 10.2% in the placebo and 11.0% in the enalapril group) or reinfarction (6-month reinfarction rates were 9% [total number 268] in the placebo and 9% [total number 271] in the enalapril group). These results do not necessarily contradict the observations from the SOLVD and SAVE trials, which did not observe differences in ischemic events until after about 6 months of treatment.

The value of ACE inhibitors initiated early in the setting of acute myocardial infarction (within 24 hours of onset of symptoms) was more recently evaluated in three very large trials: the fourth International Study of Infarct Survival (ISIS-4),[154] the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3),[155] and the Chinese Captopril Trial.[156] Preliminary results of the mortality data from these trials were recently presented. The ISIS-4 investigators reported that 2062 of 29 022 patients (7.1%) treated with captopril within 24 hours of the onset of symptoms died within 35 days of sustaining an acute myocardial infarction versus 2213 of 29 021 patients (7.6%) allocated to placebo (absolute risk reduction, 5.2 ± 2.2 per 1000; $P<.02$). This benefit appeared to widen with time and was estimated at 6.5 ± 2.8 after 6 months of follow-up. In the GISSI-3 trial, after 42 days of follow-up there were 597 deaths in 9435 patients (6.3%) treated with lisinopril compared with 673 deaths in 9460 patients randomized to placebo (7.1%) ($P=.03$). Although the benefits observed with the early use of ACE inhibitors in these very large clinical trials were small, it is important to emphasize that the reduction in mortality occurred in the presence of other interventions proven to improve the early outcome of these patients, such as thrombolytic therapy and β-blockers; the eligibility criteria for these studies were wide, and duration of treatment was only a few weeks. The Chinese Captopril Trial is not yet completed, but preliminary results indicate a favorable trend. Table 4 shows the results of these large trials, summarizing data from more than 90 000 patients randomized to ACE inhibitor therapy or placebo in the early phases of acute myocardial infarction. A small but statistically and clinically significant benefit is observed. The benefits, however, appear to be larger (about 10 lives prolonged for every 1000 patients treated) in high-risk patients (eg, those with anterior infarction, previous infarction, or heart failure at entry).

These trials provide convincing evidence for the benefit of treatment with ACE inhibitors early in the course of acute myocardial infarction, which is likely to be due to hemodynamic effects. However, they do not address whether further major ischemic events will be prevented by these drugs because of their short duration of treatment.

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TABLE 4. ACE Inhibitors in Suspected Acute Myocardial Infarction: Short-term Mortality in Large Trials

Trial	ACE-I	Duration of Follow-up, d	Deaths/No. of Patients on ACE-I (% Deaths)	Deaths/No. of Patients on Placebo (% Deaths)	Odds Ratio (95% CI)	P
ISIS-4*	Captopril	35	2062/29 022 (7.1%)	2213/29 021 (7.6%)	0.93 (0.87, 0.99)	.02
GISSI-3	Lisinopril	42	597/9435 (6.3%)	673/9460 (7.1%)	0.88 (0.79, 0.99)	.03
Chinese Captopril Trial*	Captopril	28	572/6321 (9.0%)	610/6308 (9.7%)	0.93 (0.87, 0.99)	NS
Consensus II	Enalapril	30	219/3044 (7.2%)	192/3046 (6.3%)	1.15 (0.94, 1.41)	NS
Combined Trials		28-42	3450/47 822 (7.2%)	3688/43 503 (8.5%)	0.93 (0.89, 0.98)	.004

ACE indicates angiotensin-converting enzyme; ACE-I, ACE inhibitor. Addition of results of seven smaller trials of ACE-I in acute myocardial infarction (129 deaths/1816 ACE-I–treated vs 138 deaths/1837 placebo-allocated patients) does not significantly change the combined estimate of ACE effect; for all combined trials, odds ratio=0.94 (95% CI, 0.89, 0.99); P (two-tailed)=.01.
*Analysis of the Chinese Captopril Trial and the ISIS-4 Trial are not fully complete, and the numbers in this table are based on preliminary reports.

Trials After PTCA

ACE inhibitors have the theoretical potential to prevent restenosis after PTCA because of the demonstrated potent antiproliferative action of these drugs on vascular smooth muscle cells and supportive data from animal studies. In the MERCATOR trial,[89] 693 patients were randomized to receive cilazapril or placebo started on the day of angioplasty and continued for 6 months. There was no effect on angiographic restenosis and clinical events at 6 months. Similar results were reported with higher doses of cilazapril in the MARCATOR[90] study. These results contrast with the efficacy of cilazapril in the prevention of restenosis after balloon injury in the rat carotid artery model[82] and the atherosclerotic rabbit iliac artery model.[83] In the animal model, treatment was initiated before PTCA, whereas in the above clinical trials, treatment was initiated after PTCA. It is likely that the very potent and complex wound-healing process after angioplasty may differ in its responsiveness to ACE inhibitors compared with coronary artery disease not affected by invasive interventions. Furthermore, although the relatively short duration of therapy and follow-up of 6 months may have been adequate to evaluate the effects on restenosis, it may have been too short to detect differences in progression of native vessel atherosclerosis. This possibility is supported by the long-term follow-up in the MERCATOR trial, which indicated a trend toward fewer clinical cardiac end points, such as death, myocardial infarction, and coronary revascularization after 12 months of follow-up in cilazapril-treated patients.[157]

Trials in Stable Angina Pectoris

Several small trials assessing the effects of ACE inhibitors on severity of angina pectoris and/or on myocardial ischemia have reported conflicting results,[158-166] with benefit in some patients and no benefit or even exacerbation of angina in others, indicating that ACE inhibitors do not have consistent antianginal effects in short-term studies. Although reductions in the incidence of myocardial infarction and cardiac death are not expected to become apparent in these small studies on the basis of sample size alone (limited power), it is also of note that these were again investigations characterized by a short duration of therapy (6 weeks to <6 months) and therefore cannot answer questions related to the long-term efficacy of ACE inhibitor therapy in preventing major acute ischemic events by mechanisms other than acute hemodynamic changes. Sogaard et al[166] evaluated the effects of captopril on spontaneous, ambulatory ST-segment depression and on exercise-induced ST-segment depression in patients with recent myocardial infarction and left ventricular dysfunction. Both ambulatory and exercise-induced ischemia were significantly decreased by treatment with captopril. Statistically significant differences in ambulatory ST-segment depression between captopril- and placebo-treated patients became apparent after 3 months of therapy and continued to widen thereafter, being more pronounced at 6 months, while differences in exercise-induced ischemia occurred only after 6 months of therapy. These results can be explained by a continued improvement in the balance between myocardial oxygen demand and supply related to myocardial remodeling resulting in decreased left ventricular volume, concomitant reduction in both preload and afterload, and increased coronary perfusion and peripheral arterial compliance. The time course of the observed changes also suggests the possibility of other anti-ischemic effects, such as direct effects of ACE inhibition on vascular remodeling, antithrombotic effects, and effects on platelet and fibrinolytic activity.

Current Ongoing Trials

Several studies are currently under way examining the "anti-ischemic" and "antiproliferative" effects of ACE inhibitors. These studies vary in design (ie, examination of lesion development or progression by angiographic or ultrasound measures or impact on clinical end points) and consequently sample size and duration of follow-up. Key aspects of these trials are summarized in Table 5.

Conclusions

In summary, there is promising information indicating a potential role for ACE inhibitors in reducing

TABLE 5. Summary of Major Ongoing Long-term Trials Examining the Effects of ACE Inhibitors on Atherosclerotic Disease Progression or Ischemic Events in Patients Without Heart Failure or Low Ejection Fraction

Trial	ACE Inhibitor	Primary Outcome	Projected Sample Size	Duration of Treatment	Contact Investigator
HOPE	Ramipril	Composite end point: cardiovascular death, myocardial infarction, and stroke	8000-9000	3.5 years	S. Yusuf T. Montague P. Sleight The Canadian Cardiovascular Collaboration
SECURE	Ramipril	B-mode ultrasound measures of carotid atherosclerosis	700	3.5 years	E. Lonn S. Yusuf
QUIET	Quinapril	A. Quantitative coronary angiographic measures of CAD progression B. Cardiac ischemic end points*	1775	3 years	B. Pitt
SCAT	Enalapril	Quantitative coronary angiographic measures of CAD progression	468	5 years	K. Teo T. Montague
PART	Ramipril	B-mode ultrasound measures of carotid atherosclerosis	600	4 years	N. Sharpe S. McMahon

ACE indicates angiotensin-converting enzyme; HOPE, Heart Outcomes Prevention Evaluation; SECURE, Study to Evaluate Carotid Ultrasound Changes with Ramipril and Vitamin E; QUIET, The Quinapril Ischemic Event Trial; SCAT, Simvastatin and Enalapril Coronary Atherosclerosis Trial; PART, Prevention of Atherosclerosis with Ramipril Therapy; and CAD, coronary artery disease.

*Composite end point including cardiovascular death, nonfatal myocardial infarction, coronary revascularization procedures (coronary artery bypass graft surgery, angioplasty, atherectomy), and hospitalization for unstable angina pectoris.

myocardial hypertrophy, vascular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis after plaque rupture. These effects may be expected to reduce the risk for major cardiovascular ischemic events. This possibility is supported by the results of several large trials in patients with left ventricular dysfunction.

It is presently not clear, however, whether this benefit is limited to patients with reduced left ventricular ejection fraction. Furthermore, mechanisms of action underlying these observed effects are not entirely clear. This potentially important action of ACE inhibitors should be further investigated both by experimental studies to further elucidate the mechanism of action of these drugs and by clinical trials in different populations of patients at high risk for cardiovascular events. If ACE inhibitors can be definitively shown to reduce the risk of major ischemic events, these drugs will be an important intervention in high-risk individuals.

Acknowledgments

This study was supported by research grants 8-11877 and 8-11793 from the Medical Research Council of Canada. Dr P. Jha is a research fellow of The Heart and Stroke Foundation of Ontario.

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KEY WORDS • angiotensin • enzymes • coronary disease • atherosclerosis

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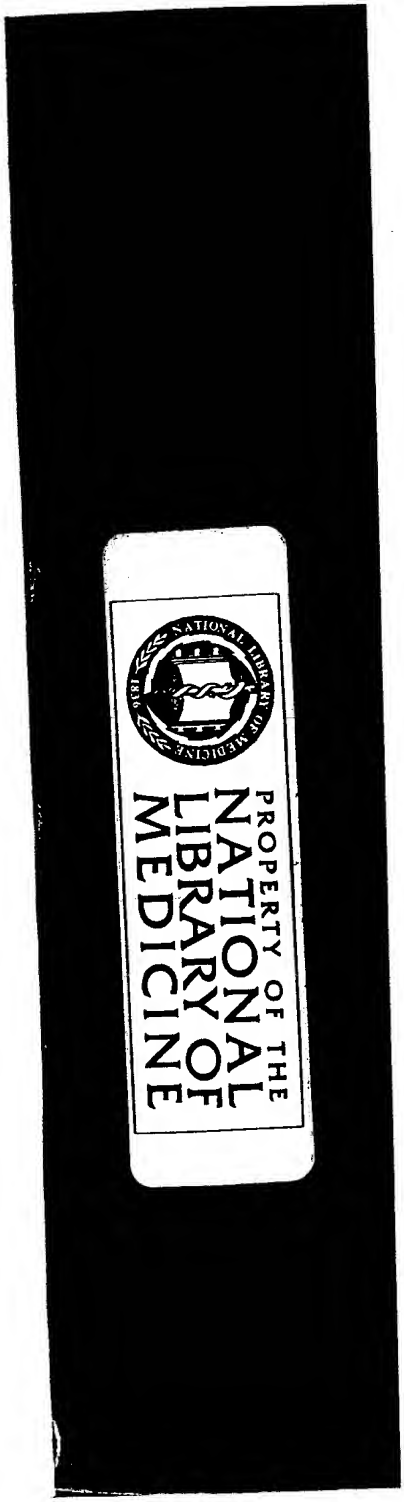
10/27/94

Circulation

American Heart Association℠
Fighting Heart Disease and Stroke

Volume 90, Number 4 October 1994



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73-3172(SP) ISSN 0009-7322

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ORIGINAL ARTICLE

Angiotensin-Converting–Enzyme Inhibition in Stable Coronary Artery Disease

The PEACE Trial Investigators*

ABSTRACT

BACKGROUND

Angiotensin-converting–enzyme (ACE) inhibitors are effective in reducing the risk of heart failure, myocardial infarction, and death from cardiovascular causes in patients with left ventricular systolic dysfunction or heart failure. ACE inhibitors have also been shown to reduce atherosclerotic complications in patients who have vascular disease without heart failure.

METHODS

In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial, we tested the hypothesis that patients with stable coronary artery disease and normal or slightly reduced left ventricular function derive therapeutic benefit from the addition of ACE inhibitors to modern conventional therapy. The trial was a double-blind, placebo-controlled study in which 8290 patients were randomly assigned to receive either trandolapril at a target dose of 4 mg per day (4158 patients) or matching placebo (4132 patients).

RESULTS

The mean (±SD) age of the patients was 64±8 years, the mean blood pressure 133±17/78±10 mm Hg, and the mean left ventricular ejection fraction 58±9 percent. The patients received intensive treatment, with 72 percent having previously undergone coronary revascularization and 70 percent receiving lipid-lowering drugs. The incidence of the primary end point — death from cardiovascular causes, myocardial infarction, or coronary revascularization — was 21.9 percent in the trandolapril group, as compared with 22.5 percent in the placebo group (hazard ratio in the trandolapril group, 0.96; 95 percent confidence interval, 0.88 to 1.06; P=0.43) over a median follow-up period of 4.8 years.

CONCLUSIONS

In patients with stable coronary heart disease and preserved left ventricular function who are receiving "current standard" therapy and in whom the rate of cardiovascular events is lower than in previous trials of ACE inhibitors in patients with vascular disease, there is no evidence that the addition of an ACE inhibitor provides further benefit in terms of death from cardiovascular causes, myocardial infarction, or coronary revascularization.

The writing committee for the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial (Eugene Braunwald, M.D., Harvard Medical School and Brigham and Women's Hospital, Boston; Michael J. Domanski, M.D., National Heart, Lung, and Blood Institute, Bethesda, Md.; Sarah E. Fowler, Ph.D., George Washington University, Rockville, Md.; Nancy L. Geller, Ph.D., National Heart, Lung, and Blood Institute; Bernard J. Gersh, M.D., Mayo Clinic Foundation, Rochester, Minn.; Judith Hsia, M.D., George Washington University, Washington, D.C.; Marc A. Pfeffer, M.D., Ph.D., Harvard Medical School and Brigham and Women's Hospital; Madeline M. Rice, Ph.D., George Washington University, Rockville, Md.; Yves D. Rosenberg, M.D., National Heart, Lung, and Blood Institute; and Jean L. Rouleau, M.D., University of Montreal, Montreal) takes responsibility for the content of this article. Address reprint requests to Dr. Braunwald at the TIMI Study Group, Brigham and Women's Hospital, 350 Longwood Ave., Boston, MA 02115.

*The investigators and research coordinators who participated in the PEACE Trial are listed in the Appendix.

N Engl J Med 2004;351:2058-68.
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BLOCKADE OF THE RENIN–ANGIOTENSIN system has been shown to prolong survival and reduce adverse outcomes in patients with systolic heart failure[1-3] or left ventricular systolic dysfunction.[4-9] Indeed, angiotensin-converting–enzyme (ACE) inhibitors have become a cornerstone in the treatment of these patients.[10-12] In addition, post hoc analyses of patients from the Studies of Left Ventricular Dysfunction (SOLVD)[13] and the Survival and Ventricular Enlargement (SAVE) trials,[5,14] both randomized studies that involved patients with moderate-to-severe left ventricular dysfunction, showed a reduction in the rate of acute myocardial infarction in patients who were treated with an ACE inhibitor. These observations raised the possibility that patients with coronary artery disease might benefit from ACE-inhibitor treatment, independently of their left ventricular function.

More recent studies have suggested that patients at high risk for coronary events indeed benefit from ACE-inhibitor therapy. In the Heart Outcomes Prevention Evaluation (HOPE)[15] and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),[16] patients with coronary or other vascular disease or with diabetes and another cardiovascular risk factor had reduced rates of death from cardiovascular causes or acute myocardial infarction when assigned to an ACE inhibitor as compared with placebo. Although both of these trials enrolled patients without a history of heart failure, many of the enrollees, especially those in the HOPE study, had an increased risk of adverse cardiovascular events.

The goal of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial was to test whether ACE-inhibitor therapy, when added to modern conventional therapy, would reduce the rate of nonfatal myocardial infarction, death from cardiovascular causes, or revascularization in low-risk patients with stable coronary artery disease and normal or slightly reduced left ventricular function.

METHODS

The design of the PEACE Trial has been described previously[17] and is summarized here. Inclusion and exclusion criteria are shown in Table 1. This study was designed by Drs. Pfeffer, Braunwald, Domanski, Geller, and Verter. The data were held and analyzed by the clinical and statistical coordinating center under the supervision of Dr. Fowler. The manuscript was written by Dr. Braunwald, Dr. Pfeffer, and the other members of the writing committee. Drs. Fowler, Pfeffer, and Braunwald take responsibility for the data presented.

CONDUCT OF THE TRIAL

Patients underwent randomization from November 1996 to June 2000 and were followed up for as long as 7 years (median, 4.8 years), until December 31, 2003. The study was conducted after approval from the institutional review boards at 187 sites (listed in the Appendix) in the United States (including Puerto Rico), Canada, and Italy. Patients gave their written informed consent to participate. An independent data and safety monitoring board reviewed patient safety data and interim results. A morbidity and mortality review committee reviewed and classified all outcomes.

In February 2002, given the increasing evidence of the benefit of ACE inhibitors or angiotensin-receptor blockers in patients with diabetes mellitus and renal disease,[18-20] the steering committee, without knowledge of the outcome data and with approval from the data and safety monitoring board, advised the investigators to substitute open-label ACE inhibitors for the masked study treatment in patients with diabetes and either overt proteinuria or hypertension and microalbuminuria.

END POINTS

Fourteen thousand one hundred patients were required to test the hypothesis that an ACE inhibitor would reduce the rate of the original primary end point, which consisted of death from cardiovascular causes or nonfatal myocardial infarction. The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or coronary revascularization. In October 1997, after 1584 patients had undergone randomization, the steering committee (without any knowledge of outcome data from the trial) concluded that recruiting 14,100 patients was not feasible and expanded the primary end point to include coronary revascularization. The sample size was reduced to 8100 patients, and the original primary end point became a secondary end point.

The study prespecified five other end points based on combinations of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, unstable angina, new congestive heart failure, stroke, peripheral vascular disease, and car-

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Table 1. Eligibility Criteria.*

Inclusion criteria
Age 50 yr or older
Coronary artery disease documented by at least one of the following:
Myocardial infarction at least 3 mo before enrollment
Coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty at least 3 mo before enrollment
Obstruction of ≥50% of the luminal diameter of at least one native vessel on coronary angiography
Left ventricular ejection fraction >40% on contrast or radionuclide ventriculography or echocardiography, a qualitatively normal left ventriculogram, or the absence of left ventricular wall-motion abnormalities on echocardiography†
Toleration of the medication and successful completion of the run-in phase, with ≥80% compliance with the medication
Exclusion criteria
Current use of or a current condition requiring use of an ACE inhibitor or a contraindication to ACE inhibitors
Current use of an angiotensin II–receptor antagonist
Hospitalization for unstable angina within the preceding 2 mo
Valvular heart disease deemed to require surgical intervention
Coronary-artery bypass grafting or percutaneous transluminal angioplasty within the preceding 3 mo
Planned elective coronary revascularization
Serum creatinine >2.0 mg/dl (177 μmol/liter)
Serum potassium >5.5 mmol/liter
Limited chance of 5-yr survival
Psychosocial condition precluding long-term adherence
Unable or unwilling to give consent
Female sex and of childbearing potential and not using contraception
Current use in a research trial of medication not approved by the U.S. Food and Drug Administration or the Health Protection Branch of the Canadian Department of National Health and Welfare

* ACE denotes angiotensin-converting enzyme.
† A subgroup of echocardiograms was reviewed by a core laboratory to confirm eligibility.

diac arrhythmia. In post hoc analyses, the primary end points of the HOPE[15] and EUROPA[16] studies, as well as new-onset congestive heart failure requiring hospitalization or causing death and new-onset diabetes, were also examined.

RECRUITMENT AND RANDOMIZATION

Potentially eligible subjects participated in a two-week run-in phase during which they were requested to take trandolapril (Mavik, Abbott Laboratories) at a dose of 2 mg per day. They were then excluded if their compliance was poor or if they had side effects or an abnormal rise in the serum concentration of creatinine or potassium. Consenting patients who successfully completed the run-in phase were randomly assigned to receive either trandolapril or a matching placebo; randomization was performed with the use of permuted blocks, stratified according to clinical site.

At a visit six months after randomization, patients who had tolerated the dose of 2 mg per day received a new six-month supply of study medication (trandolapril at a dose of 4 mg per day or matching placebo). Patients continued to be evaluated at six-month intervals for primary and secondary end points and for compliance with their assigned drug regimen. The patients, investigators, and staff members remained blinded to the treatment assignments.

STATISTICAL ANALYSIS

With the revised sample size, the trial had 90 percent power to detect an 18 percent relative reduction in the incidence of the primary end point, assuming a 19 percent cumulative incidence of the revised primary end point in the placebo group, when the log-rank test was used at a 0.05 level of significance. The sample-size calculation, based on the method of Shih,[21] assumed a 15 percent rate of discontinuation of active treatment and a 15 percent rate of crossover to active treatment.

The data and safety monitoring board reviewed data related to safety and the primary end point with use of the Lan–DeMets procedure[22] and an O'Brien–Fleming spending function to control the type I error[23] and recommended continuation of the trial until its scheduled conclusion. Statistical analyses of the primary and secondary end points followed the intention-to-treat principle. Relative risks, heterogeneity among strata, and interactions between treatment assignment and covariates were assessed by proportional-hazards regression.[24] All reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 8290 patients who underwent randomization, 4158 were assigned to receive trandolapril and 4132 matching placebo. All but one patient in each group began taking the assigned study medication. Eleven patients (three in the trandolapril group and eight in the placebo group) received study medication but did not return for a follow-up visit. The median follow-up period was 4.8 years in each group.

Most baseline characteristics were similar in the two treatment groups (Table 2). Overall, the patients' mean (±SD) age was 64±8 years and 18 percent were women. Fifty-five percent had had a myocardial infarction, 72 percent had undergone at least one coronary-revascularization procedure, and

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Table 2. Baseline Characteristics of the Patients.*

Characteristic	Trandolapril (N=4158)	Placebo (N=4132)
Age (yr)	64±8	64±8
Age >75 yr (% of patients)	11	11
Female sex (% of patients)	19†	17
White race (% of patients)‡	92	93
Country (% of patients)		
United States and Puerto Rico	58	58
Canada	30	30
Italy	12	12
Medical history (% of patients)		
Documented myocardial infarction	54	56
Coronary disease on angiography	61	61
Angina pectoris	70	71
Percutaneous coronary intervention	42	41
Coronary-artery bypass grafting	38	40
Percutaneous coronary intervention or coronary-artery bypass grafting	72	72
Diabetes	18†	16
Hypertension	46	45
Diabetes with a history of hypertension or diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg	12	11
Stroke or transient ischemic attack	7†	6
Current cigarette smoking	14	15
Blood pressure before run-in phase (mm Hg)		
Systolic	134±17	133±17
Diastolic	78±10	78±10
Diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg (% of patients)	42	41
Laboratory values		
Serum creatinine (mg/dl)	1.0±0.2	1.0±0.2
Serum cholesterol (mg/dl)	192±39	192±40
Ejection fraction (%)§	58±10	58±9
Ejection fraction >40% and <50% (% of patients)§¶	15	15
Medications (% of patients)		
Calcium-channel blocker	36	35
Beta-blocker	60	60
Aspirin or antiplatelet medication	90	91
Lipid-lowering drug	70	70
Diuretic agent	13	13
Digitalis	4	4
Antiarrhythmic agent	2	2
Anticoagulant	5	5
Insulin	4	4

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
† P<0.05 for the comparison with placebo.
‡ Race was self-declared.
§ Data on ejection fraction were available for 3952 patients in the trandolapril group and 3926 patients in the placebo group.
¶ Four patients had ejection fractions between 30 percent and 50 percent.

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17 percent were known to have diabetes. A quantitative ejection fraction was available for 95 percent of the cohort, and the mean value was 58±9 percent; for the others, a two-dimensional echocardiogram was reported as showing normal left ventricular function on qualitative assessment. Seventy percent of patients were using lipid-lowering drugs. The average serum cholesterol concentration was 192 mg per deciliter (5 mmol per liter).

FOLLOW-UP

All patients were followed until the trial closeout period (July 1, 2003, to December 31, 2003), until death, or until they became lost to follow-up. Patients were considered lost to follow-up if they had not been seen at a visit within one year before the end of the study. One hundred thirty-four patients (68 in the placebo group [1.6 percent] and 66 in the trandolapril group [1.6 percent]) were lost to follow-up. Overall, vital status was known for all but 45 (0.5 percent) of the patients who underwent randomization.

COMPLIANCE

Among the patients who were randomly assigned to the trandolapril group, 81.9 percent were taking trandolapril or an open-label ACE inhibitor at one year, 78.5 percent were doing so at two years, and 74.5 percent were doing so at three years. Among the patients randomly assigned to the placebo group, 1.5 percent were receiving an ACE inhibitor at one year, 4.6 percent were doing so at two years, and 8.3 percent were doing so at three years; 68.6 percent of the treated group and 77.7 percent of the placebo group were taking the target dose of 4 mg of trandolapril or placebo, respectively, per day. Of the 2118 patients with diabetes at baseline or new-onset diabetes by February 1, 2002, 402 (19.0 percent) had taken an open-label ACE inhibitor before February 1, 2002; 286 (13.5 percent) did so for the first time after that date.

EFFECTS ON BLOOD PRESSURE

The mean blood pressure on entry into the study (before the run-in phase) was 133±17/78±10 mm Hg in the two groups combined. After 36 months, the pressure had decreased by 1.4±0.3/2.4±0.2 mm Hg in the placebo group and by 4.4±0.3/3.6±0.2 mm Hg in the trandolapril group. The changes in systolic and diastolic pressures were significantly different between the two groups at 36 months ($P<0.001$).

PRIMARY END POINT

The incidence of the primary end point was 22.5 percent in the placebo group and 21.9 percent in the trandolapril group (hazard ratio in the trandolapril group, 0.96; 95 percent confidence interval; 0.88 to 1.06; $P=0.43$) (Table 3 and Fig. 1). Adjustment for baseline characteristics (age, sex, and the presence or absence of a history of myocardial infarction, stroke or transient ischemic attack, or diabetes) did not alter the results.

No benefit in terms of the primary end point was observed among patients assigned to trandolapril in any subgroup defined according to age; sex;

Table 3. Incidence of the Primary End Point and Its Components and of Death from All Causes.*

Outcome	Trandolapril (N=4158)	Placebo (N=4132)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary (death from cardiovascular causes, nonfatal MI, CABG or PCI)†	909 (21.9)	929 (22.5)	0.96 (0.88–1.06)	0.43
Death from cardiovascular causes	146 (3.5)	152 (3.7)	0.95 (0.76–1.19)	0.67
Nonfatal MI	222 (5.3)	220 (5.3)	1.00 (0.83–1.20)	1.00
CABG	271 (6.5)	294 (7.1)	0.91 (0.77–1.07)	0.24
PCI†	515 (12.4)	497 (12.0)	1.03 (0.91–1.16)	0.65
Death from noncardiovascular or unknown causes	153 (3.7)	182 (4.4)	0.83 (0.67–1.03)	0.09
Death from any cause	299 (7.2)	334 (8.1)	0.89 (0.76–1.04)	0.13

* CI denotes confidence interval, MI myocardial infarction, CABG coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† PCI included laser revascularization.

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race; the presence or absence of a history of myocardial infarction or of a previous revascularization procedure; the presence or absence of diabetes; the serum cholesterol or creatinine concentration; left ventricular function; or the baseline use of diuretic agents, digitalis, aspirin or antiplatelet medication, beta-blockers, calcium-channel blockers, or lipid-lowering drugs. A slight benefit was observed among patients in the trandolapril group in whom the systolic pressure before the run-in phase was less than 140 mm Hg and the diastolic pressure less than 90 mm Hg (hazard ratio as compared with placebo, 0.88; 95 percent confidence interval, 0.78 to 0.99); no benefit was observed among patients in whom the systolic pressure before the run-in phase was 140 mm Hg or higher or the diastolic pressure 90 mm Hg or higher (hazard ratio as compared with placebo, 1.09; 95 percent confidence interval, 0.94 to 1.25; P=0.02 by a test for interaction). When data for all the patients who received an open-label ACE inhibitor were censored, the hazard ratio for the primary end point in the trandolapril group was 0.95 (95 percent confidence interval, 0.89 to 1.02; P=0.16). The results did not change when data from patients with diabetes were censored at the time they began receiving ACE inhibitors on an open-label basis.

SECONDARY END POINTS AND OTHER OUTCOMES

The estimated hazard ratios for all the prespecified secondary end points in the trandolapril group, as compared with the placebo group, ranged from 0.95 to 0.98, and none were statistically significant (Table 4). Diabetes, although it was not a prespecified end point and although the analysis was not adjusted for multiple comparisons, developed in fewer of the patients assigned to receive trandolapril than of those assigned to receive placebo. In addition, fewer patients in the trandolapril group than in the placebo group were hospitalized with or died of congestive heart failure.

SIDE EFFECTS

Side effects leading to discontinuation of the study medication occurred in 6.5 percent of the patients in the placebo group and 14.4 percent of those in the trandolapril group (P<0.001). The rates of cough (39.1 percent vs. 27.5 percent, P<0.01) and syncope (4.8 percent vs. 3.9 percent, P=0.04) were greater in the trandolapril group than in the placebo group. Angioedema occurred in five patients in the placebo group (two receiving ACE inhibitors on an open-label basis) and eight patients in the trandolapril group.

DISCUSSION

In the PEACE Trial, 8290 patients with stable coronary artery disease and normal or near-normal left ventricular function were randomly assigned to receive placebo or trandolapril, and no significant differences in the primary end point — a composite of death from cardiovascular causes, nonfatal myocardial infarction, or revascularization — or in prespecified secondary end points were observed. In this trial, the ACE inhibitor trandolapril was used at the dose that had been shown in the Trandolapril Cardiac Evaluation (TRACE) Study[7] to improve survival and reduce the rate of cardiovascular events and to reduce blood pressure in trials involving subjects with hypertension.[25] Compliance with the study medication in the PEACE Trial was similar to that in other long-term trials of ACE inhibitors: slightly less than 80 percent of the patients assigned to take an ACE inhibitor and about 5 percent of those assigned to take placebo were receiving active treatment at two years. Randomization to trandolapril was associated with a clear and sustained reduction of 4.5 mm Hg in systolic pressure, as compared with randomization to placebo, in which a reduction of 1.5 mm Hg was observed. It was also associated, in a post hoc analysis, with re-

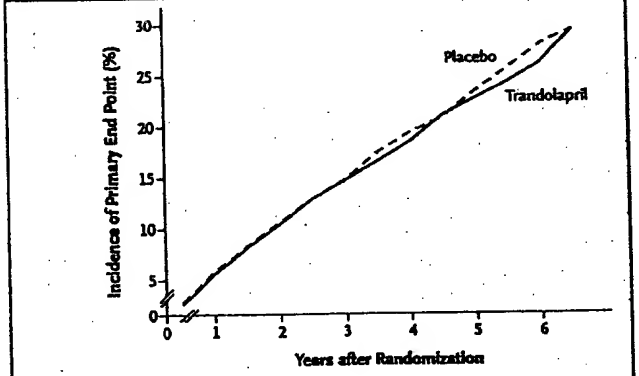

Figure 1. Cumulative Incidence of the Primary End Point, According to Treatment Group.

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Table 4. Incidence of Secondary End Points and Other Outcomes.*

Outcome	Trandolapril (N=4158)	Placebo (N=4132)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Planned analyses				
Death from cardiovascular causes, nonfatal MI, revascularization, or unstable angina	1060 (25.5)	1068 (25.8)	0.98 (0.90–1.07)	0.64
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, or new CHF	1091 (26.2)	1122 (27.1)	0.96 (0.88–1.04)	0.30
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF requiring hospitalization, or stroke	1125 (27.1)	1164 (28.2)	0.95 (0.88–1.03)	0.23
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF requiring hospitalization, stroke, or peripheral vascular disease requiring intervention, angioplasty, bypass surgery, or aneurysm repair	1205 (29.0)	1243 (30.1)	0.95 (0.88–1.03)	0.23
Death from cardiovascular causes, nonfatal MI, revascularization, unstable angina, new CHF, stroke, peripheral vascular disease, or cardiac arrhythmia requiring hospitalization	1284 (30.9)	1311 (31.7)	0.96 (0.89–1.04)	0.35
Death from cardiovascular causes or nonfatal MI (original outcome in PEACE Trial)	344 (8.3)	352 (8.5)	0.97 (0.83–1.12)	0.67
Post hoc analyses				
Death from cardiovascular causes, nonfatal MI, or stroke (outcome in HOPE)	396 (9.5)	420 (10.2)	0.93 (0.81–1.07)	0.32
Death from cardiovascular causes, nonfatal MI, or cardiac arrest (outcome in EUROPA)	346 (8.3)	356 (8.6)	0.96 (0.83–1.12)	0.62
CHF				
As primary cause of hospitalization or death	115 (2.8)	152 (3.7)	0.75 (0.59–0.95)	0.02
As primary cause of hospitalization	105 (2.5)	134 (3.2)	0.77 (0.60–1.00)	0.05
As primary cause of death	15 (0.4)	25 (0.6)	0.59 (0.31–1.13)	0.11
Stroke	71 (1.7)	92 (2.2)	0.76 (0.56–1.04)	0.09
Onset of new diabetes†	335 (9.8)	399 (11.5)	0.83 (0.72–0.96)	0.01

* CI denotes confidence interval, MI myocardial infarction, CHF congestive heart failure, PEACE the Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial, HOPE the Heart Outcomes Prevention Evaluation,[18] and EUROPA the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease.[16]

† The analysis included 3432 patients in the trandolapril group and 3472 patients in the placebo group and excluded patients with diabetes at baseline.

ductions in the number of patients in whom diabetes developed and the number who required hospitalization for the management of heart failure, as has been observed with other ACE inhibitors.[4,18] These findings provide strong evidence of the pharmacologic activity of the standard dose of trandolapril (4 mg per day).

The SAVE[5] and the SOLVD[2,4] trials demonstrated that ACE-inhibitor therapy reduced mortality and the rate of development or intensification of heart failure in patients with symptomatic heart failure and those with asymptomatic left ventricular dysfunction. Despite the use of different ACE inhibitors and inclusion criteria, both trials reported the same intriguing secondary finding — that the rate of subsequent myocardial infarction was approximately 20 percent lower among patients randomly assigned to the ACE inhibitor than among those assigned to a placebo.[5,13,14] These results suggested that inhibition of the renin–angiotensin system may produce beneficial effects with respect to atherosclerotic events. Since both of these trials were conducted in patients with impaired left ventricular function and presumed activation of the renin–

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angiotensin system, the applicability of these findings to populations of patients with normal left ventricular function remained conjectural.

Accordingly, three trials were conducted to test the hypothesis that inhibition of the renin–angiotensin system with an ACE inhibitor in patients with vascular disease who do not have overt heart failure reduces the risk of major atherosclerotic events. In HOPE, high-risk patients with vascular disease (including coronary artery disease) or diabetes who did not have heart failure and were not known to have a low ejection fraction were randomly assigned to receive either ramipril or placebo. The trial showed a significant reduction (22 percent) in the primary end point — death from cardiovascular causes, nonfatal myocardial infarction, or stroke — with ramipril.[15] Subsequently, the American Heart Association modified secondary-prevention guidelines, recommending that ACE inhibitors be "considered for all patients with vascular disease."[26]

In EUROPA, patients with stable coronary artery disease who did not have clinical evidence of heart failure and who were at a lower risk than the patients in HOPE were randomly assigned to receive perindopril or placebo.[16] The patients assigned to the ACE inhibitor had a significant reduction (20 percent) in the primary end point — death from cardiovascular causes, nonfatal myocardial infarction, or cardiac arrest. Thus, EUROPA showed that the clinical benefits of ACE inhibitors could be extended to a population of patients with coronary artery disease who had a better prognosis than those in HOPE.

In the third trial (the PEACE Trial, the subject of the current report), 8290 patients with stable coronary artery disease and normal or near-normal left ventricular function were randomly assigned to receive trandolapril or placebo; ACE-inhibitor therapy was not found to have a significant benefit. No clinical benefit was observed in the trandolapril group despite the reduction in blood pressure in that group. To interpret the predominantly negative findings of this study in the context of the positive reports from both HOPE[15] and EUROPA,[16] it is useful to compare the characteristics of the patients and the rates of events in those two trials with those in the PEACE Trial (Fig. 2). At baseline, the patients in the PEACE Trial had an average left ventricular ejection fraction of 58 percent, and their average creatinine and cholesterol concentrations were normal. Their average blood pressure at baseline was 133/78 mm Hg, which was the level

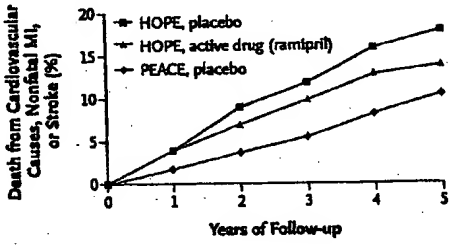

Figure 2. Comparison of Outcomes in the PEACE Trial and HOPE.
PEACE denotes the Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial, HOPE the Heart Outcomes Prevention Evaluation, and MI myocardial infarction.

achieved with use of an ACE inhibitor in both HOPE and EUROPA.

The patients in the PEACE Trial also received more intensive management of risk factors than did those in HOPE and EUROPA. At baseline, 70 percent of the patients (as compared with 29 percent in HOPE and 56 percent in EUROPA) were receiving lipid-lowering therapy. Moreover, 72 percent of the patients in the PEACE Trial, as compared with 54 percent in EUROPA and 40 percent in HOPE, had undergone coronary revascularization before enrollment; this more aggressive strategy might have contributed to the lower risk of adverse events in the PEACE Trial. Therefore, it is not surprising that with more intensive treatment of coronary artery disease and risk-factor modification, adverse cardiovascular outcomes in patients assigned to placebo were substantially lower in PEACE than they were in the other two trials. Indeed, among patients assigned to take placebo, the fractions of deaths that were deemed of cardiovascular cause also reflect this difference, at 63 percent in HOPE, 59 percent in EUROPA, and 47 percent in PEACE, as compared with 35 percent in a general population matched according to age and sex with the PEACE Trial cohort.[27] Furthermore, despite objective evidence of coronary artery disease among patients in the PEACE Trial and a history of myocardial infarction in 55 percent of them, the annualized rate of death from all causes was only 1.6 percent, similar to that of an age- and sex-matched general population.[27]

Thus, we hypothesize that the PEACE Trial does not demonstrate the benefits of ACE inhibition

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shown by HOPE and EUROPA because the patients enrolled in the PEACE Trial were at lower risk for cardiovascular events. This conclusion can be attributed in part to their baseline characteristics, including the documented absence of clinically significant left ventricular dysfunction as well as the prior use of procedures and therapies and in part to ongoing medical management. Indeed, the event rates in the placebo group in the PEACE Trial were not only lower than those in the placebo groups in HOPE or EUROPA; they were also lower than the event rates in the ACE-inhibitor groups in those two previous trials.

The PEACE Trial demonstrates that in a population of patients with coronary artery disease and preserved ejection fraction who receive intensive current standard therapy, usually including coronary revascularization and lipid-lowering agents, and in whom the rate of cardiovascular events is therefore already quite low, there appears to be no evidence of cardiovascular benefit from the addition of ACE inhibitor therapy. Therefore, ACE inhibitors may not be necessary in all such patients to reduce the risk of death from cardiovascular causes, nonfatal myocardial infarction, or coronary revascularization. However, physicians may still wish to consider ACE-inhibitor therapy for any patient who does not clearly fit the profile of patients in this trial.

Supported by a contract (N01HC65149) from the National Heart, Lung, and Blood Institute and by Knoll Pharmaceuticals and Abbott Laboratories, which also provided the study medication.

Dr. Braunwald reports having received research grant support and lecture fees from Bristol-Myers Squibb and Merck; Dr. Hsia grant support from Novartis; Dr. Pfeffer grant support and lecture fees from Novartis, as well as lecture fees from Bristol-Myers Squibb and Pfizer; and Dr. Rouleau consulting fees from Novartis and lecture fees from Pfizer and Novartis. Brigham and Women's Hospital has been awarded patents regarding the use of inhibition of the renin–angiotensin system in selected survivors of myocardial infarction; Drs. Pfeffer and Braunwald are among the coinventors. The licensing agreement with Abbott and Novartis is not linked to sales.

APPENDIX

The following investigators and research coordinators participated in the PEACE Trial (the complete list is available at http://www.bsc.gwu.edu/peace/): *Executive Committee* — E. Braunwald (co-chair), M.A. Pfeffer (co-chair), M. Domanski, S. Fowler, M. Rice, Y. Rosenberg; *Steering Committee* — Members of the Executive Committee and M. Dunlap, G. Flaker, N. Geller, B. Gersh, A. Goldberg, J. Hsia, M. Limacher, A. Maggioni, P. Mills, J. Rouleau, J. Warnica, A. Wasserman; *Sponsor* (National Heart, Lung, and Blood Institute, Bethesda, Md.) — M. Domanski (project officer), Y. Rosenberg (co–project officer), N. Geller, P. Mills; *Clinical and Statistical Coordinating Center* (George Washington University, Rockville, Md.) — S. Fowler (principal investigator), P. Cleary, N. Close, T. Davey, J. Green, J. Hsia (Washington, D.C.), K. Jablonski, D. Mason, S. Pakalapati, M. Rice, J. Verter, A. Wasserman, J. Weir, V. 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